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(54) Title: HUMAN AMINOPEPTIDASE P GENE

(57) Abstract

Disclosed are the human aminopeptidase P cDNA and genomic DNA. Also disclosed is the human aminopeptidase P protein and antibodies reactive with human aminopeptidase P. These molecules, and derivatives of these molecules, are useful for assay for detecting aminopeptidase polymorphisms, protein variants, and activity, and identifying compounds that inhibit expression of aminopeptidase genes and activity of aminopeptidase protein.

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HUMAN AMINOPEPTIDASE P GENE

Cross Reference to Related Application

This application claims benefit of U.S. Provisional Application No. 60/057,854, filed September 2, 1997.

Background of the Invention

Evidence of an aminoacylproline hydrolase was first encountered in studies of the metabolism of bradykinin (BK). It was found that BK (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) is inactivated virtually quantitatively during a single passage through the rat pulmonary vascular bed (1,2). BK is degraded through 5-8 half-lifes during the 2-3 sec required for a single transit from the right to the left side of the heart (31). If, as appears to be the case, the overall metabolism occurs within the pulmonary capillary bed (mean transit time of about 0.2 sec), the half-life of BK within the capillary bed is on the order of 0.03 sec. From these data, it was postulated that the relevant kininase enzymes are situated on, or near, the luminal surface of pulmonary endothelium so as to have access to intravascular substrates (1,2,4). In time, it was shown that angiotensin converting enzyme (ACE) plays a central role in the inactivation of BK and is, in fact, disposed on the luminal surface of pulmonary microvascular endothelium (5,6). ACE was found to account for one of the hydrolytic reactions (cleavage of the Pro^7-Phe^8 bond) observed in the earliest studies (2).

The original data indicated that a peculiar aminopeptidase also participated in the degradation of BK (1,2). The result caused some concern and confusion in that none of the aminopeptidases then known was capable of hydrolyzing an imido bond (Arg^1-Pro^2). Shortly thereafter, an aminoacylproline hydrolase was isolated from an extract of *E. coli* and was shown to be capable of hydrolyzing polyproline and the Arg^1-Pro^2 bond of BK (204,205). The bacterial enzyme was named aminopeptidase P, a name now used for aminoacylproline hydrolases obtained from any animal or plant source.

Shortly after the discovery of *E. coli* AmP, it was found that pig kidney extracts contained a particulate-associated AmP activity and that the

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AmP-like substance was not solubilized by detergents (78). The AmP-like material, believed to have been solubilized in a butanol/aqueous solvent system, behaved like a complex mixture of substances on chromatography. As a further complication, pig kidney AmP did not hydrolyze polyproline, the substrate used to assay *E. coli* AmP. A weakly reactive synthetic substrate was prepared, Gly-Pro-Hyp, and AmP activity was measured in terms of the rate of formation of free glycine in a two-step assay protocol (78).

Membrane-associated AmP remained effectively inaccessible to conventional chemical and biochemical analysis until the early 1990's. The difficulties of AmP catalytic assay was solved by preparing the synthetic substrate Arg-Pro-Pro-[^{3}H]benzylamide (APPBz-^{3}H) (20 Ci/mmol), a substrate related to the N-terminal tripeptide of bradykinin (21,22). APPBz-^{3}H proved to be highly reactive with AmP and could, by virtue of its high specific radioactivity, be used under conditions of first order enzyme kinetics. However, the problem of the inefficient solubilization of particulate-associated AmP was not solved, and a search for soluble forms of AmP was therefore conducted. Guinea pig serum was found to be an enormously rich source of AmP (21,22) and was used as the starting material to obtain apparently homogeneous AmP in two isoforms, Mr 89,000 and 81,500 (22).

Independently, Hooper *et al* (111) solved the problem of solubilizing pig kidney AmP. They found that AmP is bound to membranes via a glycosyl phosphatidylinositol (GPI) lipid anchor and can be solubilized efficiently using phosphatidylinositol-specific phospholipase C (PI-PLC). Subsequently, Simmons et al (180) and Ryan, et al. (32) showed that rat and bovine lung and guinea pig lung and kidney forms of AmP are solubilized by PI-PLC. Human kidney AmP is also solubilized by PI-PLC. Once thus solubilized, AmP no longer behaves anomalously on conventional chromatography matrices.

Aminopeptidase P (AmP; EC 3.4.11.9) is the only known human enzyme capable of hydrolyzing a N-terminal imido bond, a bond common to

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many collagen degradation products and some neuropeptides, cytokines and vasoactive peptides (14,16,21,22,31,98,111,146,147,152,165,192,205). AmP occurs in cell membrane-bound and intracellular soluble forms and is not uniformly distributed among tissues nor among cell-types of a given tissue (21,39,165,205), which implies that physiologic roles of AmP are determined by anatomic disposition (a determinant of reaction conditions and access to substrates) as well as by catalytic selectivity.

It is therefore an object of the present invention to help define both molecular and anatomic determinants of AmP functions.

Summary of the Invention

The genomic DNA and full-length cDNA sequence of human kidney AmP has been determined. The deduced amino acid sequence indicates that AmP is a member of the recently-recognized "pita bread-fold" protein family, a family of very little sequence homology but of high similarity in three-dimensional structure (59). Within the "pita bread-fold" family, there is a subdivision called the "proline peptidase" family, with which human kidney AmP shares at least five short blocks of amino acid sequences of fair to high homology (although overall homologies are low). These blocks are known to contain the amino acid residues that compose the catalytic site of *E. coli* methionine aminopeptidase, a metallo-peptidase whose structure has been determined by x-ray crystallography (59). Based on these comparisons, it is postulated that human kidney AmP amino acid residue H430 serves as the proton shuttle, and D450, D461, H520, E555 and E569 (see SEQ ID NO:2) are the catalytic metal ligands. This can be tested by preparing the site-specific mutants H430F, D450N, D461N, H520F, E555Q and E569Q. In addition, each of five potential N-glycosylation sites and each of five C residues can be mutated to examine for indirect effects of glycosyl groups and disulfide bonds on catalytic activity, solubility and protein stability. In addition, one can determine the chromosome location of AmP.

Using the sequence and immunocytochemistry at the level of electron microscopy (EM), one can define, in major organs, the cellular and subcellular sites of AmP, and, using subcellular fractions, dispositions of

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AmP in terms of anatomically proximate receptors and cell signaling molecules (the bradykinin B2 receptor, eNOS and guanylate cyclase) whose activities may directly or indirectly be affected by AmP activities.

This will help characterize structure-function relationships of human AmP at three levels: 1. molecular structure/catalytic activity, 2. cellular and subcellular distributions that determine orientations (and access to substrates) of the catalytic site, and 3. disposition in respect to "nearest-neighbor" effector and cell signaling molecules.

In addition to providing conceptual advances in understanding of AmP functions, this work provides tools (antibodies and oligonucleotide probes) useful for clinical studies of AmP deficiency states.

Use of the cDNA, genomic DNA, or a combination, for protein expression has commercial implications. The inferred amino acid sequence can be used as a starting point for defining higher structure and function. Through protein expression, crystals can be prepared for determination of higher structure. Reverse transcriptase-polymerase chain reactions was used to obtain four overlapping fragments of AmP cDNA. The intact full-length cDNA can be obtained by ligation. The first (nt 1-474) and second (359-734) fragments are digested with XmnI (nt 365) and then ligated. The product (1-734) and the third fragment (634-1702) are digested with SacI (nt 652) and ligated to yield 1-1702; which, with the fourth fragment (1588-3428), are digested with ScaI (nt 1625) and ligated to yield 1-3428. DNA encoding human AmP can also be produced by direct synthesis of appropriate oligonucleotides based on the disclosed amino acid and nucleotide sequences. For large scale protein expression, the full-length DNA is transferred into the expression vector pVL1393 and used with co-transfectant, Baculogold, in the baculovirus/Sf9 insect cell system. This system has the capacity to produce recombinant AmP in the amounts needed for x-ray crystallography. Knowledge of cellular and subcellular sites of AmP will be predictive of the consequences of specific peptidase deficiency or inhibition. Membrane-bound forms appear to be disposed as ectoenzymes, which can be verified by EM immunocytochemistry. Soluble

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AmP is believed to be disposed in as yet unknown intracellular sites. Actual dispositions can be determined as a means of defining functional roles of AmP: AmP disposed in the endoplasmic reticulum of, for example, lymphocytes is expected to have functions and reaction conditions different from ectoenzyme forms disposed on renal proximal tubule and small intestine brush border epithelia and different yet again from AmP disposed on the luminal surface of vascular endothelium.

Oligonucleotide probes and primers can be used to identify patients with homozygous or heterozygous AmP deficiencies. Primers can be used to examine for faulty AmP mRNA. Two pediatric patients with apparent homozygous deficiencies have been identified, at least one of which was mentally-retarded, epileptic and microcephalic. Early gene therapy could moderate any central nervous system injuries attributable to the lack of AmP, if administered early enough. Prenatal diagnosis of an AmP deficiency state would help decision making by parents and health care providers.

As a member of the so-called "pita bread-fold" protein family, human AmP has a recognizable putative proton shuttle and five putative metal ligands. With molecular modelling, and expressed protein, one can design inhibitors of AmP. Since AmP inactivates the blood pressure-lowering oligopeptide bradykinin, inhibitors of AmP could be useful as antihypertensive agents. Bradykinin is reported to be antimitogenic and antiatherogenic. Thus, inhibition of AmP (and concomitant preservation of bradykinin) should be useful in preventing or limiting arterial stenosis or restenosis and development of atherosclerosis. By similar means, the structure of AmP can be used to design synthetic substrate, which in turn can be used to develop diagnostic assays based on AmP catalytic activity. These substrates and others will be of value, along with recombinant AmP, for screening of drugs designed to inhibit AmP.

Since AmP is a protease capable of hydrolyzing N-terminal imido bonds it should be useful in degrading industrial protein feedstocks to free amino acids, and in breaking down wastes that have significant protein content, especially proline-rich collagenous protein wastes (wastes that are

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otherwise resistant to degradation by better-known enzymes such as trypsin and chymotrypsin). In so-called intestinal malabsorption syndromes, patients are sometimes given encapsulated digestive enzymes to improve breakdown of foodstuffs. AmP should be a beneficial additive to the mix of encapsulated enzymes to facilitate breakdown of proline-rich peptides.

Human AmP cDNA and genomic DNA can be used for designing antisense oligonucleotides, which may, in turn, be useful in patients having a surplus of AmP that, for example, contributes to arterial stenosis or restenosis or that contributes to development of atherosclerosis. By analogy with uses of AmP inhibitors, some downward modulation of AmP activity via use of antisense nucleotides might provide antihypertenstive effects.

There are now some highly reliable computer programs that can identify peptide sequences within the primary structure of a protein that are likely to be immunogenic. Such programs can be used to identify immunogenic sequences within the inferred human AmP structure. Thus, knowledge of the nucleotide sequence of human AmP cDNA and genomic DNA can lead to the design of synthetic "epitopes" and preparation of highly specific polyclonal and monoclonal antibodies. Antibodies are useful in the development of immunoassays having diagnostic uses. Alternatively, recombinant expression of AmP protein clearly provides an appropriate antigen for preparing specific antibodies to AmP.

Human AmP cDNA and genomic DNA can be used to develop transgenic animal models and can be used, under low stringency conditions, to clone AmP cDNAs and genomic DNAs of other animal species. By the latter means, knockout animal models can be prepared and provided commercially to other investigators. The AmP cDNA and genomic DNA can also be used to prepare stable transformants that can be provided commercially to other investigators. With knowledge of the AmP DNA sequence and its coding for putative critical amino acid residues of the catalytic site, mutants can be prepared to modulate catalytic activity. Similarly, unglycosylated, truncated forms of AmP can be expressed that are catalytically active but more amenable than wild-type AmP to crystallization.

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Such forms should be highly useful to drug design firms.

The DNA of a functionally related enzyme, angiotensin converting enzyme (ACE), is known to be polymorphic, and one form is associated with high levels of serum ACE. Human AmP cDNA and genomic DNA can be used to examine for polymorphisms, which, if found, can be further studied for functional impacts.

Brief Description of the Drawing

Figure 1 is a comparison of the amino acid sequence of human aminopeptidase P to porcine amino peptidase P.

Detailed Description of the Invention

History of Isolation and Physiological Roles of AmP

Using guinea pig serum AmP as immunogen, mouse polyclonal and then monoclonal antibodies, which were found to bind guinea pig and rat lung and kidney forms of AmP at high affinity, were prepared. One of the monoclonal antibodies, HL510, also binds human AmP (32). The anti-AmP preparations have proved to have many uses and have been particularly helpful in immunoaffinity chromatography. Immunoaffinity chromatography has substantially simplified the task of purifying AmP and yields apparently pure AmP in the mole quantities needed for structure studies. HL510 has also been used for light microscopy immunocytochemistry. In guinea pigs, spleen, kidney, liver, lungs and small intestine are particularly rich sources of catalytically-active immunoreactive AmP.

Extensive amino acid sequencing using guinea pig lung and kidney forms of AmP were performed. Protein and cDNA databases were searched. It was found that guinea pig AmP contains at least three of six blocks of highly conserved sequences characteristic of a recently recognized group of proteins called the proline peptidase family. The match of primary structures appears to have functional significance in that all family members (e.g. human proline dipeptidase) are, like mammalian AmP, capable of hydrolyzing imido (as opposed to amido) bonds. The conserved blocks provided a simple guide for cloning AmP cDNA because one could then

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specify, in terms of block placements (e.g. block C within the middle of AmP and block F near the C-terminus), pairs of primers that would yield large or small stretches of cDNA.

Recently, pig kidney cortex AmP has been sequenced almost completely (Edman degradation and some mass spectroscopy) (196). In addition, AmP and the entire proline peptidase family have been postulated to be members of a larger protein family ("pita bread-fold" family) not characterized by common functions but by highly similar 3-dimensional structures. Using these new findings and our data, human kidney AmP cDNA was clone. Unexpectedly, the primers prepared originally to correspond with guinea pig lung AmP sequences worked as well with human kidney mRNA.

In addition, the database searches made evident that AmP has a clinical relevance greater than previously supposed. A Medline search of the biochemistry of human proline dipeptidase (PDP) raised several apparently relevant issues. For example, PDP deficiencies are well-documented and appear to be caused by several different gene defects, including single base mutations and inappropriate splicing (83,84,187,188). Both protein-positive and protein-negative PDP deficiency states have been described. It is therefore believed that the genetics of PDP deficiencies will provide a guide for searches for AmP deficiencies. It was also found that AmP deficiencies have been reported and can have clinical expressions like those seen in PDP deficiencies. Blau *et al* (62) found two boys of consanguineous parents who excreted in urine a mixture of proline-containing oligopeptides, including Gly-Pro, a dipeptide excretory product characteristic of PDP deficiency. However, the boys excreted in greater amounts (up to 30 mg/day) a tetrapeptide, Gly-Pro-Hyp-Gly, not seen in urines of normal subjects nor patients with PDP deficiencies. It was determined that the excreted tetrapeptide has a sequence identical to the N-terminal tetrapeptide of a putative hormone called antiarrhythmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (51-56). In the characterization of guinea pig serum AmP (21,22), it has been found that AmP binds AAP at high affinity *in vitro*. Gly-Pro-

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Hyp-Gly is among the commonest tetrapeptide sequences of collagen, and its excretion in urine of an AmP-deficient patient may reflect failure in late stage collagen metabolism and amino acid conservation.

In addition, Blau *et al* (62) found that an intestinal biopsy sample obtained from one patient contained saccharase and PDP activities within the normal range but did not contain AmP catalytic activity (less than 2% of the normal mean). Both of the patients were mentally-retarded. One, in addition, had microencephaly and epilepsy. Mental retardation is also a characteristic of PDP deficiency (84,187,188). It may be relevant to both deficiency states that AmP and PDP occur in rat cerebral cortex, largely in association with astrocytes (98,147,148). It may also be relevant that astrocytes appear to 'guide' vasculogenesis in retina (30) and perhaps in other parts of the central nervous system. AmP-related mental retardation may result in part from deficient vasculogenesis in early development of the central nervous system.

In rat lungs, AmP and ACE together account for all of the bradykinin-inactivating activity. This result initially appeared to be inconsistent with the fact that five of the eight peptide bonds of BK are hydrolyzed during passage through the rat pulmonary vascular bed (1,2,14). However, biologically-inert metabolic fragments of BK are not, *a priori*, invulnerable to proteolytic attack. Indeed, one pulmonary endothelial peptidase, dipeptidyl peptidase IV (DP IV), cannot hydrolyze BK (124,199) but can rapidly degrade the BK fragments formed by AmP (e.g. des-Arg^1-BK) to release Pro-Pro. Pro-Pro is a BK metabolite. It thus appears that three of the five hydrolytic reactions occur after BK has been inactivated by AmP and/or ACE. Recently, Simmons and colleagues (120) have confirmed these findings and have shown that combined inhibition of ACE and AmP has profound blood pressure lowering effects in renin-related hypertension (119).

There are large interspecific differences in distributions of AmP. AmP occurs in abundance in guinea pig and rat kidneys and lungs but is virtually absent from rabbit and cat kidneys and lungs (16). In fact, human

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tissues were found to have AmP in relatively high abundance (Table 1). By Northern blot analysis, human kidney, liver, small intestine, heart, lung, colon and placenta are particularly enriched in AmP mRNA (47).

Table 1 Relative abundance of aminopeptidase P mRNA in various human tissues

Tissue	Relative intensity
Kidney	100
Lung	32
Heart	42
Placenta	16
Liver	55
Small Intestine	55
Colon	21

This information can be used to a) relate molecular structure to AmP catalytic activity, b) define its cellular and subcellular dispositions so as to clarify orientations of the catalytic site, and c) define the anatomic relationships of AmP to functionally-related "nearest-neighbor" effector and cell signaling molecules.

The underlying hypothesis is that roles of AmP in systemic biochemistry are likely to be determined by reaction conditions, access to substrates and responses of "nearest neighbors" (all set by anatomical relationships) as well as by catalytic selectivity. Thus, AmP disposed near cell matrix may be well-positioned to participate in secondary, tertiary or higher stages of collagen metabolism, AmP disposed on intestinal brush border epithelium likely functions as a specialized digestive enzyme, AmP disposed on renal proximal tubule epithelium plausibly participates in conservation of proline, AmP in neuronal tissues may process neuropeptides, and AmP disposed on vascular endothelium processes circulating peptide hormones such as bradykinin (31,34,39,181). It has been suggested that soluble forms of AmP disposed in platelets and lymphocytes may act to modulate effects of cytokines and peptides that mediate acute inflammation (165,191,192,205).

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As noted above, two pediatric patients with AmP deficiencies have been identified, both mentally-retarded (62). Whether mental retardation can be attributed to AmP deficiency is not yet clear, but the possibility should be testable in that the cloned human AmP cDNA provides a guide for preparing AmP knockout mice. Similarly, there is a basis for blocking AmP expression in rats by use of antisense AmP oligonucleotides. Rat AmP cDNA can be cloned using human AmP cDNA, or fragments, as a probe.

Both AmP-deficient patients excreted oligopeptides having N-terminal Xaa-Pro- residues, and these peptides (most notably Gly-Pro-Hyp-Gly) may most directly reflect the AmP deficiency state. AmP should degrade the latter peptide to form Gly plus Pro-Hyp-Gly. The latter is a substrate for DAP IV, and the expected dipeptide, Pro-Hyp, is a substrate for proline dipeptidase (PDP). Normally, human renal proximal tubule contains AmP, DAP IV and PDP in abundance (110), and the three enzymes may constitute a cascade of reactions important for amino acid conservation.

Homozygous AmP deficiencies are probably rare. Partial AmP deficiencies may be relatively common, a possibility that has been suggested *vis a vis* a side effect of angiotensin converting enzyme (ACE) inhibitor therapy (31): ACE inhibitors are widely-used for the treatment of hypertension and congestive heart failure (93). Most patients experience few, if any, side effects. However, a small percentage of patients develop urticaria and angioedema (99), problems that can also occur when bradykinin is infused i.v. in relatively high doses (66). It appears that AmP is normally the last defense against the entry of BK into the systemic arterial blood of patients treated with ACE inhibitors (31). Clearly, patients with a relative or complete AmP deficiency could be at exceptional risk if treated with an ACE inhibitor. When angioedema affects tissues of the upper airway, thereby obstructing air flow, death can occur within minutes. Therefore, even though angioedema is an uncommon side effect of ACE inhibitors, it would be worthwhile to determine its molecular basis. If an AmP deficiency underlies ACE inhibitor-induced angioedema, a pretreatment test for the deficiency

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could spare some patients from life-threatening ACE inhibitor-induced angioedema.

Using the AmP catalytic assay described herein and the knowledge that human plasma, platelets, lymphocytes and urine (all being readily accessible biopsy tissues) normally contain AmP catalytic activity (21,106,165,191,205), untreated hypertensive patients can be screened now for AmP deficiencies. Antibodies to human AmP and genetic probes can be produced. Thus, AmP deficiency states, protein-positive and protein-negative, and their bases at the molecular level can all be determined.

Molecular structure and function

Purification of aminopeptidase P.

Three groups independently purified aminopeptidase P (AmP) to apparent homogeneity. As noted above, guinea pig serum is a rich source of soluble AmP, which can be purified to obtain two isoforms, Mr 89,000 and 81,500 (22). On concanavalin-Sepharose chromatography, both isoforms were found to behave as a mixture of biantennary and high mannose glycoproteins (70%/30%). Turner and colleagues (111) purified pig kidney cortex AmP, after converting the amphipathic into the hydrophilic form with phosphatidylinositol-specific phospholipase C (PI-PLC), to obtain an apparent single isoform, Mr 95,000, that was converted by treatment with N-glycosidase F into two isoforms, Mr 71,500 and 68,000. Simmons and Orawski (180) purified bovine lung AmP, solubilized with PI-PLC, which on SDS-PAGE migrated at Mr 95,000. All three purifications were laborious and required seven or more steps. The Turner protocol employed nine steps and provided apparently pure AmP in a 1% yield (111). Guinea pig, pig and bovine forms of AmP all behaved as if N-blocked on Edman degradation.

To obtain a simpler means of purifying AmP, two mice were immunized with the biantennary form of guinea pig serum AmP. Both mice produced high titer anti-AmP, which, on Western blotting, proved to be reactive with both AmP isoforms, Mr 89,000 and 81,500. The spleen of one mouse was used to produce hybridomas, twelve of which produced anti-AmP, all of the IgG_1 isotype. A hybridoma that produced anti-AmP with

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anticatalytic effects on reaction with guinea pig serum, rat kidney and human serum AmPs, was selected. After double cloning, ascites monoclonal antibodies, known hereinafter as HL510, was produced.

HL510 was used to prepare an immunoaffinity matrix (antibody bound to protein A-Sepharose and then crosslinked with a bifunctional active ester). The immunoaffinity matrix enabled isolated of homogeneous guinea pig AmP in the quantities needed for amino acid sequencing and was used to purify hydrophilic (post-PI-PLC treatment) forms of kidney and lung AmP as well as serum AmP. A 4 ml column of the matrix was used repeatedly to obtain a total of about 20 nmol of apparently pure AmP.

Others tried to purify soluble "cytosolic" forms of AmP. Harbeck and Mentlein (98) obtained highly-purified rat brain AmP, which behaved on molecular sieving (Mr 143,000) as if a dimer of the Mr 71,000 monomer found on SDS-PAGE under reducing conditions. Whether brain AmP is an unglycosylated alternative gene product related to gpi-anchored AmP is not yet clear. The profile of rat brain AmP in terms of selectivity of substrate hydrolysis and responses to inhibitors and other affectors is similar to those of kidney, lung and serum AmPs, and alternative splicing of the primary transcript may account for the apparent absence of gpi-anchoring. However, it has been reported that some strains of *E. coli* contain two AmP products and two separate genes (206), which may also be the case for human AmPs.

Soluble forms of AmP have also been purified from human platelets (191) and leukocytes (165). Both AmPs migrate on SDS-PAGE at Mr 71,000. On molecular sieving, platelet AmP behaves as a trimer (Mr 223,000) and leukocyte AmP behaves as a dimer (Mr 140,000). No direct studies have been performed to clarify glycosylation, but human platelet AmP was not retained by a mixed concanavalin A/wheat germ lectin chromatography matrix.

Sequencing.

Guinea pig AmP behaved on Edman degradation as if N-blocked. LysC digests of both kidney and lung AmP were therefore prepared, and the peptide products separated on Tris-tricine gels (79,172). Partial digestion

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conditions were used to generate relatively large fragments. Separated peptides were blotted to a Problott membrane (ABI), and three lung and four kidney AmP fragments were selected for sequencing. Where overlaps occurred (80 amino acid residues), lung and kidney AmPs were found to be identical in structure.

The "BLAST" network (49,50) was used to look for possible similarities to known proteins. The search picked up a tentative match with human proline dipeptidase (PDP). A second search using the "BLOCKS" program (102) revealed that guinea pig AmP contains at least three of six highly conserved blocks of amino acid sequences that define a newly-recognized protein family called the proline peptidase family. Further details on how guinea pig kidney and lung AmPs line up with sequences of known members of the proline peptidase family (of which PDP is a member) were obtained using the program "IALIGN" (77). Through the foregoing analysis, it was evident that guinea pig kidney and lung AmPs contained all of proline peptidase blocks C,E and F.

The six conserved blocks in human prolidase (blocks A-F) are arranged alphabetically from the N-terminus. By comparison with human PDP, the order of sequenced fragments of guinea pig kidney and lung AmP was deduced. Importantly, the expected length of protein between the fragments could be estimated, keeping in mind that the number of residues between conserved regions in AmP are not the same as found for other members of the family (blocks E and F are fused in AmP but are separated by more than 20 amino acid residues in PDP) (83,84). This information reduced the number of PCR primers that one would need to test and provided clues for analyzing PCR data. Knowledge of the placement of blocks of conserved sequences also provided clear directions for the use of nested primers.

The proline peptidase group is a small family of related proteins including *E. coli* aminopeptidase P II, *E. coli* proline dipeptidase and human proline dipeptidase (PDP; prolidase). All three of these proteins are classified as manganese metalloenzymes, primarily because they are

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stimulated by Mn^{2+}. In this regard, mammalian AmP is also stimulated by Mn^{2+} in its reaction with some, but not all, substrates (22, 31, 32, 111, 152, 180). Zinc, 0.2 mole, was reported to be present per *E. coli* AmP subunit as detected by atomic absorption spectrophotometry (206), and pig kidney AmP is reported to contain about 1 mole of Zn per mole of enzyme (108). Finding a match of guinea pig lung AmP with human PDP was intriguing because of their similarity in substrate selectivity. Proline dipeptidase cleaves imide bonds of dipeptides in which proline is C-terminal, whereas AmP acts as an aminoacylproline hydrolase (22,29,32,83,188).

Matthews and colleagues solved the three-dimensional structure of *E. coli* methionine aminopeptidase (AMPM) by x-ray crystallography (59). They began a database search for sequence-relatives and found 12 other proteins with small blocks of fair sequence similarity. One sequence-relative was found to be *P. putida* creatinase (CREA), another protein whose three-dimensional structure is known. Although the primary sequence homology between AMPM and CREA is low, Matthews and coworkers found that each protein possessed a C-terminal domain disposed in a "pita bread" fold. 218 C^{α} atoms of each protein are superimposable to within 2.5 Å. Further examination of the primary sequences of other sequence-relatives of AMPM (including AmPs of *E. coli*, *S. lividans* and *M. tuberculosis*) revealed, in each case, $\alpha\alpha\beta\beta\beta$ sequences characteristic of "pita bread" folds. Of no less importance, binding sites for the catalytic divalent metal of AMPM were well-characterized and were known to be disposed on either side of a two-β-sheet cleft common to AMPM and CREA. Based on the homologous tertiary structural blocks of the AMPM "pita bread" family and their similarities to at least four of the conserved blocks of the proline peptidase family in combination with the sequence data, one could predict part of the tertiary structure of guinea pig AmP and identify at least four of the metal-binding amino acid residues of the catalytic site; all without knowing the complete amino acid sequence. Block C clearly is within a β-sheet of the catalytic crevice and contains two divalent metal ligands (later identified in human kidney AmP as D450 and D451; see below), and blocks E and F are

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clearly part of an apposing β-sheet and contain two more metal ligands (E555 and E569 in human AmP).

Dr. Wolfram Schäfer of the Max-Planck-Institut für Biochemie sequenced most of pig kidney AmP by Edman degradation and some mass spectrometry (196). Within the limits of the sequence data, guinea pig and pig AmP sequences are 93% identical and 98% highly homologous.

The data on human AmP, with those of Matthews and colleagues (59) and Schäfer and colleagues, makes evident that mammalian AmPs contain the six conserved blocks characteristic of the proline peptidase family and that all known members of the proline peptidase family in fact compose a subgroup of the AMPM/CREA family of proteins characterized (not by their functions but) by their "pita bread" tertiary conformations. Blocks A and B of proline peptidases are parts of exterior α-helices and blocks C, D, E and F are parts of the two apposing β-sheets that contain the catalytic site. With the primary sequence of human kidney AmP (see SEQ ID NO:2), the catalytic metal binding sites could be assigned: block C, D450 and D461; block D, H520; block E, E555; and block F, E569. A putative proton shuttle, H430, could also be postulated. Each of the putative divalent metal-binding ligands and the putative proton shuttle is a reasonable target for preparing site-specific mutants.

Human kidney AmP cDNA.

There are large interspecific differences in AmP abundance and distributions among organs (16,21). Using human kidney and lung poly A RNAs in reverse transcriptase polymerase chain reaction (RT-PCR) studies with degenerate guinea pig primers, five cDNA fragments whose nucleotide sequences enabled preparation of nondegenerate primers for human AmP cDNA were obtained.

A sense primer based on QMDCNW (now known to be residues 124-129 of human AmP) was used with a reverse primer based on FQKEAY (residues 474-479) to obtain a 1068 bp fragment. Fragments from three separate PCR reactions were subcloned (TA Cloning Kit, Invitrogen) and sequenced. All three independent PCR products were found to have

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identical sequences, ruling out PCR nucleotide-incorporation errors. The remaining 5′ and 3′ nucleotide sequences were obtained by RACE methods. 5′-RACE was performed using both human kidney and lung poly A RNAs. PCR products were subcloned and sequenced. Kidney and lung cDNA sequences were identical for the N-terminal open reading frame plus 264 bases of the 5′-untranslated region. 3′-RACE was performed to obtain the C-terminal portion of AmP coding sequence plus a 1145 base 3′-untranslated region. Two independent reactions gave identical sequence results.

Composite cDNA and amino acid sequences.

The composite cDNA sequence is shown in SEQ ID NO:1. The DNA sequence has an open reading frame of 2019 nucleotides. The deduced amino acid sequence (SEQ ID NO:2) comprises 673 residues with a calculated molecular weight of 75,490. Comparison of the human AmP amino acid sequence to that of the pig (reported by Turner, 113) shows evolutionary divergence with only 83% amino acid sequence identity between the two species (Figure 1). Five of six potential N-glycosylation sites found in the pig sequence at residues 34, 48, 64, 277, 290, and 294 are conserved in the human sequence at residues 35, 49, 65, 278, and 291. Five of six cysteine residues that are potentially involved in disulfide bond formation are also conserved. These are located in the human sequence at positions 36, 127, 294, 299, and 531. By comparison of the human AmP amino acid sequence with that of *E. coli* methionine aminopeptidase (59), it is postulated that, for human AmP, H430 is the proton shuttle and D450, D461, H520, E555 and E569 are the catalytic metal ligands. Site-specific mutants can be used to test this and to determine placements of disulfide bonds. Potential N-glycosylation sites can be mutated to examine for effects on AmP solubility and stability.

Because AmP is a GPI-anchored protein, it is expected that the mature protein can be derived from a nascent form containing N- and C-terminal signal peptides that are removed during processing in the endoplasmic reticulum. Based on the weight-matrix method of von Heijne, analysis of the pig sequence (113) suggests that the N-terminal cleavage site

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is either Lys-24 or His-22. The most important sequence positions in the von Heijne method are those at -1 and -3. If Lys-24 represents the true cleavage site this would put Pro at the -1 position in the pig sequence which is unusual in eukaryotic signal sequences. Lys-24 and His-22 are both conserved in the human sequence as are the -1 and -3 positions relative to His-22 (Figure 1). The -3 position relative to Lys-24 is also conserved. The -1 position, however, contains a Thr residue rather than a Pro which is more commonly found in this position in eukaryotic signal sequences. Based on the cleavage prediction criteria developed by Udenfriend and Kodukula (61), Ala-649 has been predicted to be the C-terminal ω-residue in the pig enzyme with Arg and Ala in the important ω+1 and ω+2 positions, respectively (113). Identical ω, ω+1, and ω+2 residues are found in the human AmP enzyme (Figure 1). The exact anchorage site can be examined by mutation and by Edman degradation and mass-spectrometry of C-terminal peptides produced by GluC digestion.

Genomic DNA Sequence of Human AmP.

A search of GenBank using the human AmP cDNA sequence revealed a sequence, dJ753P9 (an unfinished human chromosome X genomic sequence from the Sanger Center group of the Human Genome project), containing human AmP sequences. A comparison of this clone with the AmP cDNA sequence revealed segments of the genomic sequence that were in the wrong orientation or relative position, or which were spurious. These errors would not have been readily apparent without comparison to the cDNA sequence. Using the cDNA sequence as a guide, the jumbled dJ753P9 sequence was rearranged to arrive at the genomic sequence of human AmP, including introns. A second sequence, dJ454M7 (a genomic sequence containing the oculocerebrorenal syndrome gene also from the Sanger Center group of the Human Genome project), overlapped the dJ753P9 sequence in the upstream region. 110,000 nucleotides of the dJ454M7 sequence was combined with the rearranged dJ753P9 sequence to arrive at the disclosed human AmP genomic sequence. The sequence data of sequences dJ753P9 and dJ454M7 were produced by the X Chromosome

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Sequencing Group at the Sanger Centre and can be obtained from ftp://ftp.sanger.ac.uk/pub/dJ753P9 and ftp://ftp.sanger.ac.uk/pub/dJ454M7, respectively.

The assembled genomic sequence is shown in SEQ ID NOs:3, 4, 5, 6, and 7. SEQ ID NO:3 shows the first 50,000 nucleotides of the AmP genomic DNA (nucleotides 1 to 50,000). SEQ ID NO:4 shows the next 50,000 nucleotides of the AmP genomic DNA (nucleotides 50,001 to 100,000). SEQ ID NO:5 shows the next 44,453 nucleotides of the AmP genomic DNA (nucleotides 100,001 to 144,453). SEQ ID NO:6 shows the next 45,546 nucleotides of the AmP genomic DNA (nucleotides 144,454 to 189,999). SEQ ID NO:7 shows the last 16,955 nucleotides of the AmP genomic DNA (nucleotides 190,000 to 206,954). SEQ ID NOs:3, 4, and 5 represent sequences upstream of the AmP coding region. SEQ ID NO:6 represents the AmP coding region (including introns) and some downstream sequences. SEQ ID NO:7 represents sequences downstream of the AmP coding region. The location of introns in the AmP genomic DNA is shown in Table 2. The position refers to the nucleotide positions in SEQ ID NO:6.

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Table 2: Intron	Location of introns in the AmP genomic DNA Position (in SEQ ID NO:6)
1	49-2893
2	2969-4749
3	4861-5990
4	6054-7023
5	7129-7382
6	7470-8394
7	8542-11255
8	11361-12535
9	12614-12936
10	13135-13947
11	14038-15260
12	15372-16083
13	16159-17270
14	17346-19969
15	20030-21300
16	21370-21959
17	22068-22796
18	22854-23481
19	23560-28390
20	28415-28418
21	28482-29079

The coding region in the exonic sequences contain a total of 2019 nucleotides, in perfect agreement with the coding region of human AmP cDNA. The cDNA sequence (SEQ ID NO:1) contains 264 nucleotides of 5' untranslated region, which starts at nucleotide 144,190 in the genomic sequence (nucleotide 44,190 of SEQ ID NO:5). The 3' untranslated region starts at nucleotide 173,725 in the genomic sequence (nucleotide 29,272 of SEQ ID NO:6). Regulatory sequences are present in the sequences upstream and downstream of the AmP coding sequence. The locations in AmP genomic DNA of restriction sites for rare-cutting restriction enzymes are shown in Table 3. The position refers to the nucleotide positions of the entire genomic sequence (1 to 206,954).

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Table 3: Locations in AmP genomic DNA of restriction sites

Enzyme	Position	Recognition sequence
I-CeuI		
I-DmoI		
I-PpoI		
I-SceI		
PI-PspI		
PI-SceI		
PI-TliI		
SfiI	28417	GGCCCTCCTGGCC
SfiI	35327	GGCCTGGAAGGCC
SfiI	59892	GGCCGCCGCGGCC
SfiI	123855	GGCCTGAGAGGCC
SfiI	127512	GGCCAAGGTGGCC
SfiI	147456	GGCCCTTGTGGCC
SfiI	163911	GGCCTCAATGGCC
SfiI	173654	GGCCGCCAGGGCC
SfiI	174720	GGCCAAATTGGCC
SfiI	191056	GGCCCCATCGGCC
SfiI	199214	GGCCACAGAGGCC
XcmI	805	CCAAGCCCTCCATGG
XcmI	3268	CCAGACCCCTGCTGG
XcmI	9208	CCACTGAAGGCTTGG
XcmI	11273	CCAGATGTGTGGTGG
XcmI	13446	CCAGTCTAACTATGG
XcmI	20139	CCATGCCCCTCCTGG
XcmI	22210	CCAGGTGAGAGGTGG
XcmI	24186	CCAGATCTCTCCTGG
XcmI	30663	CCAAAGCAATCCTGG
XcmI	33277	CCAGCCCGGCCATGG
XcmI	34994	CCAGGCAATGGCTGG
XcmI	38816	CCAGTGGTCTTCTGG
XcmI	41331	CCATGTCTCAATTGG
XcmI	43990	CCATTGTGGCTATGG
XcmI	44005	CCATGCCTAGTCTGG
XcmI	51655	CCAAGGAATGGCTGG
XcmI	54873	CCAGGAGGGGGGTGG
XcmI	55199	CCAAGACAAGCCTGG
XcmI	56459	CCAGCCGGGCCCTGG
XcmI	57685	CCAAGGACAAAGTGG
XcmI	59638	CCAGCCGCCCCATGG
XcmI	62439	CCAATCCTTGATTGG

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Table 3 continued.

XcmI	63335	CCATAACAGCTATGG
XcmI	64615	CCACGTCTCTTGTGG
XcmI	68860	CCAGTTCCGTTATGG
XcmI	69175	CCACAAACTTCGTGG
XcmI	71843	CCACTGGTTTGGTGG
XcmI	74250	CCACTTTTTGATTGG
XcmI	82876	CCAGTATCTCAGTGG
XcmI	84993	CCATGCCTGATCTGG
XcmI	85463	CCAGGGGAGAAATGG
XcmI	91933	CCAGGGTTGGTGTGG
XcmI	93853	CCAATCACAGGGTGG
XcmI	101230	CCATCATTTTCTTGG
XcmI	101577	CCACCAACTGGGTGG
XcmI	102163	CCAAGAAGCACCTGG
XcmI	104088	CCACAAGGCTCTTGG
XcmI	105177	CCATAGACTGGGTGG
XcmI	106153	CCAGCCCCACTATGG
XcmI	106482	CCAGGGGCTTGTTGG
XcmI	106541	CCAGTGGAGGCCTGG
XcmI	106612	CCAGTGCAAGAGTGG
XcmI	107121	CCAAGGATGAGATGG
XcmI	110156	CCAGCTCAGCCTTGG
XcmI	110232	CCAACTGACCAGTGG
XcmI	112312	CCATCTGTCTGCTGG
XcmI	120228	CCAAGCACAGGATGG
XcmI	121774	CCATTGGCCACTTGG
XcmI	124227	CCATCCTCTCCCTGG
XcmI	129232	CCAATTCTTTCTTGG
XcmI	130760	CCATATGTCCCCTGG
XcmI	131995	CCAAGCCACATCTGG
XcmI	132931	CCAGCCAGCAATTGG
XcmI	132981	CCAGCACCGACTTGG
XcmI	133432	CCAGAGAGGGGCTGG
XcmI	133986	CCACCCCATCTATGG
XcmI	135217	CCAATGAGAACATGG
XcmI	156250	CCAGGGACCCACTGG
XcmI	158121	CCAGAGTGCTGGTGG
XcmI	158928	CCAAATTATTCCTGG
XcmI	159043	CCAATTCCTAACTGG
XcmI	159777	CCAAAGGCACAGTGG
XcmI	165124	CCACATCGCCTCTGG
XcmI	166087	CCACAGCAATTATGG
XcmI	167088	CCAGAGCCAATCTGG

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Table 3 continued

XcmI	169063	CCATAAACAACATGG
XcmI	173427	CCATCTGGACTATGG
XcmI	174118	CCAAGGGTGCCATGG
XcmI	178624	CCAGGCCGGGCATGG
XcmI	178990	CCAAGGCCTTCCTGG
XcmI	182319	CCAGCAAGGACCTGG
XcmI	182870	CCAAAGGCCCGATGG
XcmI	183061	CCAAAGAATGTATGG
XcmI	184682	CCATAGTGACAATGG
XcmI	185891	CCACTTTGGCCATGG
XcmI	185967	CCAACCTGGAGATGG
XcmI	185992	CCATTCCAGTCTTGG
XcmI	186440	CCAGGTGCCCTATGG
XcmI	188286	CCACTTTCTCCATGG
XcmI	193275	CCAGCTCCCCCGTGG
XcmI	195033	CCACTGAGGCAGTGG
XcmI	199546	CCAAACTGACCATGG
XcmI	204870	CCAACTTGACTGTGG

Tissue Distribution Determined by Northern blots.

The expression of membrane-bound AmP mRNA in human tissues was examined by Northern hybridization analysis of poly $(A)^+$ RNA (Clontech) using the 1068 bp human AmP cDNA fragment. A single 3.5 kb message was detected in human kidney, lung, heart, placenta, liver, small intestine, and colon. No transcript was detected in Northern analysis of poly $(A)^+$ RNA from human brain, skeletal muscle, pancreas, spleen, thymus, prostate, testis, ovary, and peripheral blood leukocytes. Possibly AmP RNA is in low abundance in the latter tissues, which can be determined by RT-PCR studies. The relationships between membrane-bound and soluble forms of AmP are unknown, but it may be relevant that heart poly A RNA gave a strong signal on Northern blotting. According to Simmons and collaborators (152), heart contains AmP in a soluble form.

Anatomic determinants of function.

Because AmP is not uniformly distributed among tissues and is apparently disposed as an ectoenzyme on some cell-types and as an intracellular enzyme in other cell-types, its roles in systemic biochemistry must be determined in part by its cellular and subcellular dispositions, distributions that restrict access to substrates and set reaction conditions.

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Reactions of AmP *in vivo*.

To gain further insight into functions of AmP in systemic biochemistry, studies were conducted to determine the physiologically-relevant question: Is BK in central venous blood hydrolyzed by pulmonary endothelial AmP *in vivo*? The immediate metabolic fate of the AmP synthetic substrate Arg-Pro-Pro-[^{3}H]benzylamide (APPBz-^{3}H) (20 Ci/mmol) during a single transit from the right heart to the left was examined. Effects of increasing quantities of carrier APPBz and alternative AmP substrates such as bradykinin (BK) and des-Arg^9-BK (31) were then measured. It was found that tracer doses of APPBz-^{3}H are extensively hydrolyzed (mean hydrolysis of about 55% during a 2-3 sec mean transit time) and that the metabolic process is saturable (carrier APPBz injected at 42 nmol/kg b.w. reduced fractional hydrolysis of coinjected APPBz-^{3}H by half). Using isolated rat lungs perfused with Krebs-Henseleit solution containing albumin, 4 g %, it was found that APPBz-^{3}H is still extensively hydrolyzed, a result to be expected if AmP is largely disposed on the pulmonary vascular surface (5,6,12,14,31,167). It was also found that carrier APPBz at 2 μmol/kg completely inhibited hydrolysis of coinjected tracer substrate and can thus be used as a short-acting AmP inhibitor. As implied by the saturable characteristics of APPBz-^{3}H hydrolysis, alternative substrates for AmP should, in saturating doses, also inhibit APPBz-^{3}H hydrolysis. In fact, BK proved to be an alternative substrate of even higher affinity than carrier APPBz: coinjected BK, at 13 nmol/kg, reduced APPBz-^{3}H hydrolysis by half. Des-Arg^9-BK was an alternative substrate of lesser affinity; ED_{50} of 107 nmol/kg. Des-Arg^1-BK is apparently not a substrate for AmP but binds to the catalytic site nonetheless (21,22,31); thus, des-Arg^1-BK coinjected with APPBz-^{3}H was expected to reduce hydrolysis of the tracer, an expectation met experimentally (ED_{50} of 30 nmol/kg).

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Potentiation of effects of bradykinin (BK).

If BK inhibits hydrolysis of APPBz-^{3}H, BK hydrolysis by AmP should be inhibited by APPBz; a possibility tested as follows: Log dose-response curves were constructed by measuring the mean systemic arterial blood pressure effects of BK injected into the superior vena cava (i.v.) or the root of the aorta (i.a.). As shown previously (1,2,161), BK is extensively degraded during passage through the rat pulmonary vascular bed. Thus, the i.v. dose of BK required to reduce arterial blood pressure by, say, 25 mm Hg is 40 or more times the i.a. dose of BK required to exert equivalent effects. To the extent that pulmonary AmP contributes to BK inactivation, saturation of AmP with an inhibitor or alternative substrate should, in effect, potentiate blood pressure effects of i.v. BK. It was found that either of carrier APPBz or des-Arg^{9}-BK potentiated blood pressure effects of i.v. BK by up to 4-fold. Effects of i.a. BK were also potentiated, a result that suggests that AmP is disposed on both pulmonary and extra-pulmonary vascular surfaces. From the relationship $PF=2^{n}$, where PF is "potentiating factor" and n is the number of biological half-lifes, it can be computed that a 4-fold potentiation of i.v. BK effects on blood pressure effects bespeaks the ability of pulmonary AmP to degrade BK through two half-lifes in a time interval of less than three sec (mean pulmonary transit time). Thus, AmP alone can degrade BK by 75%.

Pulmonary angiotensin converting enzyme (ACE) is a major contributor to BK inactivation (119,120,167). Inhibition of ACE potentiates blood pressure effects of i.v. BK by 40- to 200-fold. The four-fold potentiation of i.v. BK effects achieved by inhibition of AmP is less spectacular but, as discussed below, important nonetheless. To clarify relative contributions of ACE and AmP to the metabolic fate of BK administered i.v., blood pressure effects of i.v. BK under control conditions and then after administration of a long-acting ACE inhibitor, RAC-X-65, were compared. After ACE inhibition, BK was injected (i.v. and i.a.) alone or BK co-mixed with APPBz at a dose capable of saturating AmP (2 μmol/kg). ACE inhibition shifted both i.v. and i.a. log dose-response curves leftward. The i.v. curves were most affected but still lay to the right

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of the i.a. curves by a factor of about four. Inhibition of both ACE and AmP caused the i.v. and i.a. BK log dose-response curves to become superimposable. The latter result appears to mean that, in rat lungs, ACE and AmP account entirely for the pulmonary metabolism of BK. When both AmP and ACE are inhibited, effects of i.v. BK are potentiated by up to 800-fold. In one experiment of this series, 2.5 ng of i.v. BK (about 2 pmol) reduced systemic arterial blood pressure by 20 mm Hg; a finding that gives new emphasis to the importance of pulmonary AmP and ACE in preventing the entry of BK into the systemic circulation under physiologic conditions.

Clinical implications.

Precisely how BK is inactivated in humans is a matter of clinical importance. BK is an edematogenic compound capable of inducing urticaria when administered i.v., and has been postulated to play a role in induction of angioedema (99). Human lungs contain ACE, which is distributed so as to have access to circulating substrates such as BK and angiotensin I (66). However, there are now several million patients under treatment with ACE inhibitors and who therefore lack the ability to inactivate BK via the ACE pathway. Available data suggest that BK does not normally accumulate to any great extent in the blood of patients treated with ACE inhibitors (157,177), which in turn suggests that there is a backup, or supplemental, system for BK inactivation. Whether AmP accounts (or accounts for a significant fraction) for BK inactivation in patients treated with ACE inhibitors is not yet known, but the possibility is worthy of consideration in terms of adverse effects of ACE inhibitors. An infrequent, but potentially fatal, adverse effect of ACE inhibition is angioedema, a complication that may be due to the lack in some patients of a non-ACE BK-inactivating system, possibly AmP. It is likely that some subjects lack AmP. Blau *et al.* (62) have reported that an intestinal biopsy sample from a 15-year-old male contained normal saccharase activity but no measurable AmP activity (less than 2% of the mean of control values). Plausibly, subjects lacking AmP activity are at risk for ACE inhibitor-induced angioedema. By analogy, a relative lack of AmP could be associated with other, more frequent, ACE

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inhibitor-related side effects such as cough and pemphigus-like skin eruptions (31,99).

Immunocytochemistry.

Functions of AmP are likely to be determined in part by its anatomic dispositions which are evident by immunocytochemistry performed at the level of light microscopy. A description of these studies follows.

Antibody specificity.

HL510 and the polyclonal anti-AmP have been used in the immunocytochemistry studies described below. Although the epitope bound by HL510 is not yet known, all data support its specificity. HL510 binds to guinea pig plasma, lung and kidney AmP isoforms and works well for immunoprecipitations, western blots and immunocytochemical studies. HL510 binds rat forms of AmP; thus, parallel studies of the disposition of AmP in guinea pig and rat tissues were conducted. HL510 has anticatalytic effects on human plasma AmP and has proved to be useful for purifying human lung AmP. HL510 reacts specifically with human pulmonary artery, lung microvascular and aortic endothelial cells as evidenced by indirect immunofluorence and immunoprecipitation studies. HL510 immunoaffinity matrix binds the two isoforms (Mr 89,000 and 76,000) of PI-PLC solubilized guinea pig kidney AmP quantitatively. Prolidase, a proline peptidase family relative of MW 56,000 (83), is not bound by the immunoaffinity matrix nor by HL510 alone as evidenced by the fact that the two kidney AmP isoforms were obtained in homogeneous forms on immunoaffinity chromatography (32) and the fact that a Mr 56,000 protein has not been found in AmP preparations collected by immunoprecipitation. Cross-reacting contaminants having Mr's like those of the AmP isoforms can also be ruled out. Eight peptides produced by LysC digestions of immunoaffinity-purified guinea pig lung and kidney AmPs have been sequenced. Each of the eight peptides sequenced as if pure (no secondary sequence signals). All of the sequences aligned with high similarity with the pig kidney AmP sequence. These results, then, are consistent with the conclusion that HL510 is specific for AmP.

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Light microscopy.

Based on the early studies of pulmonary angiotensin converting enzyme (ACE) (5,6), glutaraldehyde fixatives were used, and the light microscopy studies using frozen sections and sections of tissues were fixed in picric acid/paraformaldehyde. The latter fixative is adequate for electron microscope (EM) immunocytochemistry at moderately high resolution (5,6). Thus, the data should be directly applicable to EM immunocytochemical studies. In addition, Vector ABC kit reagents were used throughout (second antibody bridged via a biotin:avidin complex to horseradish peroxidase), and these too can be used for some EM studies.

As shown in micrographs, the entire alveolar-capillary unit of guinea pig lung appears to react with anti-AmP. This is a picture essentially identical to that obtained in light microscope immunocytochemistry studies of pulmonary ACE (69), a target known to be disposed almost exclusively on the luminal surface of pulmonary endothelial cells (5,6). Resolution at the EM level will therefore be required to determine precise cellular and subcellular dispositions of AmP. It is very likely relevant, however, that the AmP immunoreactivity of the arteriole shown in the left upper quadrant of a crograph is restricted to the endothelial layer. Initially, it was believed that AmP would co-localize with ACE, given the facts that 1) ACE is disposed on endothelium and 2) both enzymes have access to peptide substrates injected i.v. (31,167). Results obtained thus far are consistent with localization of AmP on endothelium. AmP immunoreactivity in association with some airway epithelial cells and mononuclear leukocytes, cell-types that are not reactive with anti-ACE, has been found. To distinguish similarities and differences in the cellular dispositions of AmP and ACE, EM studies are planned in which tissue is examined using both mouse anti-AmP and rabbit anti-ACE. AmP, unlike ACE, is believed to participate in the metabolism of collagen fragments formed by collagenase (205), thus whether AmP is disposed in, or near, intercellular matrix can be determined.

Micrographs show that AmP immunoreactivity is also disposed on guinea pig renal proximal tubule, jejunum enterocytes and villus vascular

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cores and in association with microvessels of the endocrine and exocrine pancreas. The kidney micrograph illustrates that cells of the glomerulus, including glomerular endothelium, lack AmP immunoreactivity. Previous studies of ACE were similar: glomerular endothelium was unique among endothelia studied in that it failed to react with anti-ACE (69). Endothelium of small arteries of the renal cortex react with anti-AmP, but by far the greatest AmP immunoreactivity is that of the proximal tubules.

Immunocytochemistry studies of rat tissues were, with one exception (see below), consistent with the studies of guinea pig tissues. Pulmonary alveolar-capillary units were heavily stained, as were airway epithelial cells. Similarly, small intestine enterocytes and kidney proximal tubules were heavily stained, and glomerular cells were apparently free of AmP immunoreactivity. However, rat spleen contained few, if any, sites of AmP immunoreactivity, whereas the red pulp of guinea pig spleen (and microvessels of red and white pulp) were heavily stained. In guinea pig spleen red pulp, cells on sinusoid walls were heavily stained, as were mononuclear leukocytes. Some human lymphocytes contain a 71,000 Mr AmP in soluble form (165), as do rat cerebral astrocytes (147). The results indicate that some guinea pig leukocytes possess AmP immunoreactivity. If the guinea pig leukocyte AmP immunoreactivity represents the soluble 71,000 Mr isoform, one can purify it using the immunoaffinity columns now on hand. Guinea pig and rat tissue homogenates were assessed for AmP catalytic activity (21,22). Rat kidney, lung and jejunum contained AmP at the highest specific activities. For guinea pig, the highest specific activities were found in homogenates of spleen, kidney, liver, and jejunum. The immunocytochemistry results are in accord with the biochemical surveys.

Immunofluorescence photographs show the reaction of HL510 with human pulmonary microvascular endothelial cells in culture. Ref. 34 contains an immunofluorescence micrograph of the reaction of HL510 with human aorta endothelial cells. Antibodies to AmP can be prepared by using as immunogens unique peptide sequences of human AmP predicted to be antigenic (EGCG program). Further to favor precise localizations,

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antibodies labeled with colloidal gold particles can be used. As a gpi-anchored enzyme, membrane-bound AmP is expected to be localized in caveolae (137,184). Indeed, the distribution of immunofluorescent spots in micrographs is typical of antigens situated in caveolae (90,91).

AmP and its nearest-neighbors.

Increasingly, it appears that cell membrane receptor/cell signaling reaction cascades depend in part on close anatomic proximity of all or many of the relevant reactants. Extensive biochemical data have revealed close associations between receptors, signaling molecules and caveolins (74,89,92,130,138,160,173,175,183). Complementary morphologic data are lacking. Specifically, subcellular dispositions of endothelial AmP in respect to effectors and signaling molecules whose functions may directly or indirectly be influenced by AmP catalytic activity can be determined. AmP in respect to the bradykinin (BK) B2 receptor, eNOS and guanylate cyclase can be determined.

As a gpi-anchored enzyme, it is anticipated that AmP is disposed within endothelial caveolae (3,4,11,74,90,137,173). Some have reported that localization of gpi-anchored proteins within caveolae is an artifact attributable to crosslinking of antigen: antibody complexes by second antibodies (143,145). However, cytochemical techniques without crosslinking agents have shown that endothelial 5′-nucleotidase, now known to be gpi-anchored, is disposed almost exclusively within caveolae (3,4). Further, coupled functions of cell membrane receptors with cell signaling proteins known to be disposed on the cytoplasmic aspect of caveolae argue in favor of anatomic proximity (9-11,63,89,127,128,164).

Given the high likelihood that AmP functions in part as a BK inactivating enzyme (31) and that BK in near-physiologic concentrations (~10 pM) exerts effects on endothelial cells (e.g. mobilization of arachidonate and synthesis of TxA_2 and PGI_2) (7-11), endothelial cells have been used in culture to examine morphologically for functionally-significant anatomic proximities of AmP with the BK B2 receptor and well-characterized BK-activated signaling molecules known to be associated with

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caveolae (90,91,131,173). A two antigen immunocytochemistry approach can be used. This should reveal aspects of AmP functions that are dependent not only on subcellular disposition but also on functionally-related proximate proteins.

AmP in human pulmonary microvascular endothelial cells.

Cultures were fixed with 4% formaldehyde, permeabilized with 0.2% Triton X-100 in BSA/PBS, incubated with primary antibody (1:100 dilution) (monoclonal anti-GP-AmP, overnight at 4°C) followed by secondary antibody (FITC-labeled goat anti-mouse IgG, 1 hour at 22°C) and then analyzed and photographed using a Biorad confocal microscope.

Transient expression of AmP in COS-1 cells.

The full length 3.5kb cDNA encoding human kidney AmP can be inserted into the expression vector pBKCMV as described for pig kidney AmP cDNA (113). The orientation of the insert can be verified by a directional PCR reaction, and the correct construct can be used to transfect COS-1 cells. About 2E + 06 cells are plated in 150 cm^2 culture flasks and allowed to proliferate for 24h at 37°C (113). Cells are then washed with OptI-Mem and transfected (5 µg of DNA/flask) using lipofectAmine. After 2h at 37°C, Dulbecco's modified Eagle's medium containing 10% FCS is added. Twenty four h later, the medium is replaced with fresh, and the cells will be incubated at 37°C for another 24h.

Parallel control cultures, transfected with vector lacking the AmP cDNA insert, can be processed similarly. A small portion of control and test cells are harvested and examined by indirect immunofluorescence using our monoclonal anti-AmP HL510 as the primary antibody. A second portion of each of the control and test cells are washed free of culture medium and then resuspended in 50 mM Hepes/NaOH buffer, pH 7.4, containing 0.15 M NaCl (assay buffer). The AmP substrate Arg-Pro-Pro-[^{3}H]benzylamide (21) is added to the cell suspension to a final concentration of 20 nM (1 µCi/ml). The cell/substrate reaction mixture is incubated at 37°C, and aliquots is collected at timed intervals for measurement of the rate of formation of the expected product, Pro-Pro-[^{3}H]benzylamide (21,22). AmP activity can be

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computed to yield the first order rate constant, Vmax/Km. COS-1 control cells (transfected with vector lacking the AmP cDNA insert) do not express AmP (113); thus we expect to be able to detect even low levels of expression of human kidney AmP.

The bulk of the COS-1 cells can be worked up to prepare cell membranes. The cells, in assay buffer containing 10 μg/ml of each of pepstatin, leupeptin and aprotinin, are homogenized, and the homogenate is subjected to differential centrifugation (32,110,111). The cell membrane-enriched fraction is assayed for AmP catalytic activity (see above), and then solubilized with 60 mM octyl glucoside (76). Half of the resulting mixture is treated with phosphatidylinositol-specific phospholipase C (recombinant PI-PLC from B. thuringiensis) before phase separation with Triton X-114, and the remaining half is directly phase separated. If, as expected, the expressed AmP possesses a glycosyl phosphatidylinositol (gpi) lipid anchor, PI-PLC treatment should convert the amphipathic form (partitioned into the Triton phase) into the hydrophilic form. Both amphipathic and hydrophilic forms are subjected to SDS/PAGE under reducing conditions (10% gel). The proteins will be transferred on to Immobilon P for western blot analysis using anti-AmP HL510. Expressed monomeric AmP is expected to have an Mr near 90,000 (22,32,111,152,180).

Overexpression of AmP.

The baculovirus/Sf9 insect cell system, a system known to be capable of expressing biologically functional, glycosylated gpi-anchored proteins, will be used to obtain human kidney AmP in milligram quantities. Recombinant human cluster of differentiation antigen CD59 has been thus obtained in milligram quantities, with not less than 98% of the product bearing the gpi anchor, as judged by Triton X-114 phase partitioning before and after treatment with PI-PLC (76). Approximately half of CD59 was anchored to the cell membrane, and the remainder was secreted into culture medium. The secreted CD59 was in amphipathic form and could be converted by PI-PLC into the hydrophilic form. CD59 was produced in three isoforms, all with the expected N-terminal amino acid sequence and all

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bearing a gpi anchor. Apparently, the glycosylation process was overwhelmed by high protein expression such that the two smaller isoforms were inefficiently glycosylated. The ability of Sf9 cells to N-glycosylate recombinant proteins at expected sites is well-recognized; however, the glycosyl groups are generally of the high mannose type (76). The efficiency of glycosylation improves with increasing time of culture, thus it may be useful to analyze samples, and harvest and replace if indicated, culture medium daily so as to collect separately secreted AmP isoforms that differ in terms of numbers and possibly types of glycosyl groups. As for glycosyl groups, the types of anchors attached to recombinant proteins are characteristic of Sf9 cells and can differ in structure from gpi anchors attached by, e.g., human kidney proximal tubule epithelial cells (76). Nonetheless, Sf9 cell-produced proteins have the expected full-length peptide, correctly folded and crosslinked by disulfide bonds. Recombinant enzymes thus produced are typically fully active (76,194,195).

Overexpression of wild-type human AmP

The cDNA sequence encoding human AmP can be subcloned into the polyhedrin-based plasmid transfer vector pVL1393 (Pharmingen). Recombinant transfer vector can then be cotransfected with Baculogold (Pharmingen) viral DNA into Sf9 insect cells (2×10^6 cells in monolayer). Six days after cotransfection, the cells can be harvested and expression of AmP examined by assay of catalytic activity, immunofluorescence and western blotting. Conditioned medium containing recombinant virus is used to reinfect Sf9 cells through 2-3 rounds of amplification to obtain a high titer virus stock (1E+08 virus particles/ml). Optimal conditions of multiplicity of infection and length of infection can be defined. Maximal expression is typically obtained after 3-4 days of infection, at which time conditioned medium can be harvested and worked up in parallel with the Sf9 cells for their contents of recombinant human AmP. Samples of conditioned medium can be collected at timed intervals before final harvest in order to monitor efficiency of glycosylation. N-glycosylation of AmP early in culture is expected to be relatively inefficient and may provide useful insights if

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multiple isoforms are obtained at final harvest. Triton X-114 phase extractions can be performed to examine for the efficiency of gpi-anchor attachments. As for recombinant human CD59, it is expected that conditioned medium will contain substantial quantities of recombinant AmP in its amphipathic form (76).

Purification of wild-type human AmP can be based primarily on the immunoaffinity procedure that we have described previously (32). However, two early group separation procedures may simplify purification and improve yields. In the first step, amphipathic protein is selected for by Triton X-114 phase separation. The Triton phase is collected, diluted and then treated with PI-PLC. In a second step, the PI-PLC-formed hydrophilic protein, expected to be N-glycosylated with high mannose side functions (76), is isolated on concanavalin A-Sepharose. AmP is eluted. The immunoaffinity purification step can then be performed using relatively low protein loads. The goal is to obtain at least 20 nmol (about 2 mg) of pure AmP per 150 cm^2 culture flask. The high titer virus stock produced as described above can be used to scale up production of recombinant AmP as needed. All of the following studies of wild-type AmP can be performed using less than 50 nmol of the pure protein.

Characterization of wild-type AmP.

Kinetics.

Using Arg-Pro-Pro-[^{3}H]benzylamide as substrate, kcat, Km and kcat/Km can be measured as described in the studies of guinea pig serum AmP (22). Pure recombinant wild-type human AmP is expected to have a second order rate constant, kcat/Km, on the order of 1.8E + 08 M^{-1} min^{-1} (22). In addition, kinetics of the reaction of AmP with bradykinin, Arg-Pro-Pro and Gly-Pro-Hyp can be characterized (22,111,180). pH optimum and pH stability studies can be performed using Mes, Hepes and phosphate buffers. Recombinant AmP can be examined for expected responses to effectors such as Mn^{2+}, EDTA, o-phenanthroline, p-hydroxymercuribenzoate, and dithiothreitol (22,111,113,152,180). Recombinant AmP can also be tested for thermal stability (152,180), not

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only for comparison against naturally-occurring AmP, but also to set a baseline for characterizing potentially unstable mutants that lack disulfide bonds, glycosylation sites or metal ligands.

Chemical properties.

Incorrect estimations of the molar extinction coefficient of angiotensin converting enzyme (ACE) caused confusion for more than a decade, especially in terms of determination of the number of atoms of zinc per molecule of ACE and the specific activity of the pure enzyme (see 27 and its references). To avoid such confusion for AmP, UV spectra (210-340 nm) can be developed using three concentrations of wild-type AmP (optical densities of about 0.2, 0.5 and 1.0 at 280 nm). To enable accurate computation of AmP concentrations, a sample of each AmP preparation thus tested can be submitted to quantitative amino acid analysis. Special focus can be placed on histidine, which is expected to be recovered in a mole ratio (His/AmP) of 12. When the molar extinction coefficient is established, it can be used to calibrate protein assay results obtainable by conventional Lowry, BCA and dye-binding methodologies.

Recombinant AmP (1 nmol in a 1 mm light path cell) can also be characterized by circular dichroism. Spectra can be recorded at 13°C using a AVIV-60DS spectropolarimeter, and, with buffer baseline corrections, relative percentages of α-helix, β-sheet, β-turn and random coil structures can be estimated using AVIV software. The major purpose of these studies is to establish a basis for detecting variations in higher structure of unstable or catalytically-inactive mutants.

Recombinant AmP can be analyzed by MALDI-TOF mass spectrometry to weigh the parent molecule and any dimer or trimer forms, and examine for characteristic fragmentation patterns that may later be useful for analyzing mutants (36,196). O-glycosidase can be used to rule in or out the presence of O-linked carbohydrate (196). The following text assumes that AmP does not contain O-linked carbohydrate, and the approach will require adjustments along obvious lines if the assumption is incorrect. At present, O-glycosylation seems unlikely in that exhaustive treatment of pig

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AmP (PI-PLC solubilized) with N-glycosidase F yields a peptide of Mr 71,000, essentially as expected for a 626 residue peptide plus a gpi-anchor remnant (196).

Human kidney AmP contains a single Asp-Pro bond (D157-P158) (see SEQ ID NO:2) that is expected to hydrolyze spontaneously under the acid conditions required to form CNBr or BNPS skatole fragments (75,126). Since its spontaneous hydrolysis could complicate early efforts to interpret peptide fragment fingerprints, hydrolysis of AmP at D157-P158 should be attempted before beginning conventional fingerprinting. As described below, several analytical advantages accrue if the D-P bond can be hydrolyzed efficiently.

Recombinant AmP, 0.1 nmol initially, is dissolved in 1 ml of 7M guanidinium chloride in 10% acetic acid adjusted to pH 2.5 with pyridine (126). The mixture is incubated at 37°C for up to 96h. At timed intervals, samples are examined by mass spectrometry and N-sequenced; the latter to monitor the rate of appearance of the new N-terminus, PFLL (residues 158-161). For the following, it is assumed for convenient discussion that K24 (probably acylated) is the first residue of mature AmP and that A649 is the last. Elsewhere, these assumptions can be tested. The expected two pieces (N-piece, residues 24-157; and C-piece, residues 158-649) should be readily separated on Sephadex G-50. If reduction is required for separation of the N- and C-pieces, this will be evidence for the presence of a disulfide bond. The N-piece contains three potential N-glycosylation sites, N35, N49 and N65, and two Cys residues, C36 and C127. The N-piece is expected to have an N-α acyl modification (22,111,180). If, in fact, the N-piece is resistant to Edman degradation, it can be digested with AspN to obtain a 43 amino acid (a.a.) residue peptide which contains C36 and potential glycosylation sites N35, N49 and N65. If, as predicted, K24 is the N-terminal residue of mature AmP, an acylated (possibly diacylated) tripeptide is expected, and its mass should reveal the identity of the acyl-function (125,154,189). If one or more of its glycosylation sites is glycosylated, the 43 residue peptide can be separated from the remainder of the AspN digest using con A-Sepharose (see

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above). If C36 and C127 are linked by a disulfide, reduction of the high mannose fraction eluted from con A-Sepharose should yield a second peptide (residues 114-157), which can be identified by mass spectrometry. Mass spectrometry of the 43 a.a. residue peptide should also suggest, in terms of actual mass versus expected mass, whether one, two or all three of the potential N-glycosylation sites are glycosylated in fact. Edman degradation should make clear whether N35 and/or N49 are glycosylated. Given its distance from the AspN-generated N-terminus, N65 can be made more effectively accessible to Edman sequencing by cleavage of the M61-Q62 bond with CNBr (41,48,49,75). The expected peptide, Q62-T74, can be weighed by mass spectrometry to determine whether N65 is or is not glycosylated (36). As is needed to isolate peptides of special interest (e.g. the AspN-generated N-terminal acyl-tripeptide) that cannot be collected on con A-Sepharose, reverse phase HPLC (Brownlee, aquapore 300) with a morpholine phosphate buffer, pH 6.5, as the mobile phase can be used (103). This system provides high resolution under conditions unlikely to damage the expected gpi-tail piece and unlikely to hydrolyze peptide bonds artifactually.

Analysis of the potential N-glycosylation sites, and possible disulfide bonds, of the acid hydrolysis-produced C-piece (P158-A625) can proceed similarly. Exhaustive digestion with GluC is expected to yield two peptides containing potential N-glycosylation sites: a 41 a.a. residue peptide containing N278 (peptide T245-E285) and an 18 residue peptide (T286-E303) containing N291 and two Cys residues, C294 and C299. If glycosylated, both peptides should be susceptible to isolation from the GluC digest on con A-Sepharose. Since high mannose glycosyl groups are expected from a baculovirus/Sf9 expression system, failure of one or both peptides to bind to con A-Sepharose is presumptive evidence of the absence of an N-glycosyl sidechain (26). If both T245-E285 and T286-E303 are isolated on con A-Sepharose, mass spectrometry can be used to verify that each of N278 and N291 is glycosylated. Edman degradation of T286-E303

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may reveal whether C294 and C299 are, or are not, linked by a disulfide bond.

GluC digestion of the C-piece (P158-A649) is expected to generate a relatively small C-terminal peptide, the last residue of which, in native AmP, is attached, via ethanolamine, to the gpi anchor (86,139-141,144,159,162). If GluC can hydrolyze an E-P bond, the C-terminal peptide is expected to be PLAA. If not, the GluC-generated C-terminal peptide is expected to be W639-A649. It should be possible to collect either peptide by immunoprecipitation. The PI-PLC-generated hydrophilic form of AmP is known to possess a C-terminal common recognition determinant (CRD) (29,32,111,113,180). PI-PLC cleaves the phosphodiester bond between inositol and the diacylglycerol, forming a 1,2-cyclic phosphate ring on the inositol residue. The cyclic inositol phosphate is highly immunogenic, and antibodies prepared against any PI-PLC-solubilized protein cross-react with this epitope (the cross-reacting determinant, CRD) (86,139,140,208). We have one such antiserum (prepared against trypanosome variant surface glycoprotein) and have shown that it recognizes the CRD of PI-PLC-solubilized guinea pig kidney AmP and with an AmP peptide generated by LysC digestion (29,32).

With the anti-CRD, one can isolate the C-terminal peptide of AmP (expected to be PLAA-CRD or W639-A649-CRD) from the above-described GluC digest by immunoprecipitation and then recover the free peptide-CRD by elution using buffer containing 1 mM 1,2-cyclic inositol phosphate (available from Sigma). By N-sequencing the recovered peptide to its ethanolamine moiety, one can establish unequivocally the exact gpi anchor attachment site. There is a caveat: the CRD is acid labile (86,140) and may be damaged during the procedure used to hydrolyze the D157-P158 bond (see above). If in fact the AmP-CRD is destroyed, AmP (not previously exposed to strong acid) can be digested, in a separate experiment, with GluC and then isolate the CRD-bearing peptide as described above.

Focus on cysteine residues.

The foregoing chemical analysis will make it clear which of the

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potential N-glycosylation sites of wild-type recombinant AmP are in fact glycosylated. As also noted, some clues may be gained on the presence and dispositions of disulfide bonds. However, unequivocal assignments of Cys residues taken up in disulfide bonding will require an independent approach, such as the following.

Native recombinant AmP, 1 nmol, in 50 mM Hepes/NaOH buffer, pH 8.3 (21,22), can be reacted with 1,000 nmol of (1-^{14}C)iodoacetamide, ~3 Ci/mol, at 25°C for 1h. Excess ^{14}C-iodoacetamide is removed by centrifugal ultrafiltration (10K NMWL) with washing. Specific radioactivity can be measured by liquid scintillation counting to estimate the number of alkylated C residues. The ^{14}C-labeled protein product can then be acid-treated to hydrolyze the D157-P158 bond (see above) and recover the N- and C-pieces (respectively, K24-D157 and P158-A649). The N- and C-pieces (with or without a reducing agent) are separated, and their specific radioactivities measured. Following procedures described above, the N-piece can be digested with AspN to yield the 43 residue peptide that contains C36 and a 44 residue peptide that contains C127. The former peptide, expected to be glycosylated, is separated from the latter on con A-Sepharose column chromatography. Each of the separated peptides can be assayed for its ^{14}C-content. If the N-piece is itself not labeled with ^{14}C, AspN digestion and subsequent studies will not be necessary.

If the C-piece of alkylated AmP is labeled with ^{14}C, the focus should be on GluC-digest peptides containing residues C294 and C299 (peptide T286-E303) and C531 (peptide A505-E534). T286-E303, if glycosylated at N291, should be easily separated on con A-Sepharose from A505-E534. If not, the 18 residue peptide should be readily separated from the 30 residue peptide by reverse phase HPLC. The separated peptides can be assayed for their contents of ^{14}C. Near-neighbor C residue pairs are often linked by disulfide bonds (185). If this is true for C294 and C299, peptide T286-E303 may be unlabeled. For reasons described below, C531 will be labeled with ^{14}C.

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A parallel experiment can be conducted in which native AmP, saturated with bradykinin (BK) (50 μM; Ki 1.1 μM (22,113)), is reacted with ^{14}C-iodoacetamide as above. AmP is not a thiol protease and is not inhibited by iodoacetamide nor N-ethylmaleimide. However, it is partially (~70%) inhibited by p-hydroxy-mercuribenzoate, even with the latter at low concentration (~10 nM) (21,22,111,180). Given that C531 is situated more or less in the middle of the putative catalytic metal ligands, D450, D461, H520, E555 and E569, it is highly plausible that p-hydroxymercuribenzoate binds to C531 and sterically hinders substrate binding and/or interferes with appropriate ligation of catalytic metal to the peptide backbone. By saturating AmP with its high affinity substrate BK, alkylation of C531 by ^{14}C-iodoacetamide should be prevented or strongly inhibited.

A third experiment can be performed in which native AmP is reacted with ^{14}C-iodoacetamide as in the first experiment. After 1h at 25°C, excess ^{14}C-iodoacetamide is removed and then the ^{14}C-labeled AmP is denatured and reduced (185). The reduced peptide is treated with vinylpyridine. The subsequent work up can proceed as in the first experiment to obtain AspN peptides of the N-piece and GluC peptides of the C-piece (pieces produced by acid hydrolysis of D157-P158). The relevant peptides can then be N-sequenced to determine which C residues were alkylated with iodoacetamide and which, after reduction, were covalently-bound to vinylpyridine.

Further studies to clarify dispositions of disulfides will depend on results obtained to this point. For example, if C531 is accessible to ^{14}C-iodoacetamide and C36, C127, C294, and C299 are modified only after reduction by vinylpyridine, the obvious possibilities for two disulfide bonds can be examined. One can analyse existing date to discern among the six possibilities (C36→C127, C36→C294, C36→C299, C127→C294, C127→C299, and C294→C299). For example, in experiments 1 and 2 after hydrolysis of the D127-P158 bond, was it necessary to add a reducing agent to separate the N-piece from the C-piece? If the N-piece and C-piece were separable without reduction, the disulfides are most likely to link C36→C127 and C294→C299. If more than one Cys is in reduced form,

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there cannot be fewer than three reduced Cys residues, in which case there cannot be more than one disulfide bond. In the latter scenario, the two disulfide-linked Cys residues can be identified as their vinylpyridine derivatives. Sturrock *et al* (185) have recently detailed a MALDI-TOF mass spectrometry approach for locating disulfide bonds which we plan to use if our simpler plans yield equivocal results. Dr. Nancy D. Denslow has recently developed a procedure in which a target protein is hydrolyzed by reacting reduced Cys residues with DTNB (36).

If C36 immediately follows an N-glycosylation site, N35, and may, if in reduced form, be sterically-hindered and inaccessible to ^{14}C-iodoacetamide, this anomalous behavior can be clarified, if encountered, by reacting AmP with N-glycanase before treatment with ^{14}C-iodoacetamide. Similarly, one can examine for sterically-hindered reduced Cys residues by titrating native and denatured AmP with Ellman's reagent (185).

Mutant forms of AmP.

The baculovirus/Sf9 expression system can also be used to produce mutant forms of AmP. The mutants are selected to help clarify catalytic function in terms of roles of the putative protein shuttle, H430, and putative catalytic metal ligands, D450, D461, H520, E555 and E569. In addition, one can examine roles played by glycosyl groups and disulfides in AmP function. Initially, site-specific mutations will be introduced into the wild-type human AmP cDNA sequence by the PCR-based splicing-by-overlap-extension technique described by Ho *et al* (105). Incorporation of the desired mutations can be confirmed by directional PCR. Mutant proteins will then be expressed in the baculovirus/Sf9 insect cell system under the conditions established for expression of the wild-type enzyme. The cells themselves will be examined by catalytic assay and immunofluorescence. Mutant proteins will be purified and analyzed as described above for wild-type AmP. All mutants will be characterized by mass spectrometry, UV spectrometry, circular dichroism, quantitative amino acid analysis and fingerprinting of peptide fragments (mass spectrometry and SDS-PAGE with and without a reducing agent). Catalytically-active mutants will be characterized to

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measure kcat, Km and kcat/Km using Arg-Pro-Pro-[^{3}H]benzylamide, bradykinin and Gly-Pro-Hyp as substrates (22,113,180). Temperature and pH stabilities will be defined (180).

The first mutant to be prepared is one in which the putative proton shuttle, H430, is replaced with F. If H430 is in fact the proton shuttle, the F430 mutant is expected to be essentially inactive. Pig kidney AmP is completely inactivated by diethylpyrocarbonate in a concentration that derivatizes two H residues per molecule of AmP (134). Activity is restored by treatment of the derivatized AmP with hydroxylamine. It is plausible that H430 is accessible to diethylpyrocarbonate.

The second mutant to be prepared is that in which the putative catalytic metal ligand H520 (also likely to be accessible to diethylpyrocarbonate) is replaced with F. One will then proceed to obtain mutants for each of the remaining putative four metal ligands as follows: D450→N, D461→N, E555→Q, and E569→Q. One will thereafter focus on obtaining mutants lacking potential N-glycosylation sites. Five mutants will be prepared: N35→Q, N49→Q, N65→Q, N278→Q and N291→Q. Our objective here is to determine whether glycosyl groups indirectly support catalytic activity, perhaps in terms of maintaining structure, stability and solubility. Should the glycosyl groups effect catalytic function little or not at all, it may be feasible in a future grant period to obtain a catalytically-active "deglycosylated" AmP amenable to x-ray crystallography analysis.

To obtain complementary data on roles of Cys residues and disulfide bonds, one will prepare five C→S mutants (C36, C127, C294, C299 and C531). Characterization of these mutants should reveal roles of disulfide bonds in maintaining higher structure. In addition, the C531→S mutant may help clarify the anomalous partial inhibition of wild-type AmP by p-hydroxymercuribenzoate (pHMB): The S531 mutant is expected to be catalytically-active and resistant to inhibition by pHMB.

One plans to use both site-specific mutation and deletion mutation to characterize the C-terminus of AmP. For example, A648 and A649 (the postulated gpi anchor attachment residue) will be replaced with R residues or

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simply deleted. These studies may also be guided by results of a parallel study. In the latter study, one plans to compare membrane-bound AmP with apparently soluble forms of AmP. AmPs in astrocytes, platelets, heart, adrenal medulla and lymphocytes appear to be soluble enzymes of cytosol (98,101,106,147,148,152,165,191,192). Conceivably, soluble AmP is the product of a different gene. However, it is also conceivable that alternative processing occurs such that, e.g., kidney and heart AmPs differ in their C-terminal sequences. To test the latter possibility, one will prepare sense primers to, with the antisense APT primer of the 3'RACE system, obtain the nucleotide sequence(s) of soluble AmP cDNA from human kidney AmP cDNA nucleotide 2070 to the poly A tail. For these purposes, one have prepared poly A RNA's of human heart, adrenal gland and brain. It may be relevant that residues 643-646 (HTEP) closely resemble a known cell retention sequence signal (HTEL) that directs some liver carboxylesterases to storage in the endoplasmic reticulum (158).

Cellular and subcellular dispositions of human aminopeptidase P.

To a large degree, the functions of AmP in integrative biology are likely to be determined by its anatomical dispositions. Like other exopeptidases, AmP is selective, but not specific, in terms of substrate hydrolysis. In these terms, anatomical distribution can be understood to restrict access of AmP to those substrates available in the cellular or extracellular compartment in which the catalytic site is disposed. Thus, AmP disposed on small intestine brush border epithelium could plausibly function as a digestive enzyme that facilitates breakdown of collagenous foodstuffs, whereas AmP disposed on renal proximal tubule epithelium may function to process filtered peptides so as to conserve amino acids and modulate effects of some peptide hormones. Thus, the first objective is to determine by immunocytochemistry at the level of electron microscopy anatomical dispositions of AmP and orientation of its catalytic site.

From another perspective, anatomical disposition of a given protein can be a determinant of secondary or tertiary reactions conducted by "near-neighbor" molecules, a concept well-recognized in terms of receptors and

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coupled signaling proteins. Given that AmP is probably disposed in part in specialized cell membrane domains (e.g. in endothelial caveolae) believed to play key roles in cell signaling (74,92,121,131,136,137,173-175), the second objective is to help define morphologically "near-neighbors" of AmP whose functions may reasonably be influenced by reactions catalyzed by AmP.

Preparation of antibodies.

Monoclonal antibody HL510, prepared against guinea pig serum AmP (22,32), is reactive with human AmP and has been used in immunofluorescence studies to localize AmP on human endothelial cells (34). In the short term, one will continue to use HL510 for immunocytochemistry; however, one will in parallel prepare antibodies against specific peptide sequences in human kidney AmP that are predicted to be highly antigenic. For the latter search, one used the EGCG program (Wellcome Trust Genome) to identify antigenic sequences (112). The goal is to obtain at least one high affinity antiserum to a known epitope that does not occur in other proteins of the "pita bread" family of proteins (59).

AmP peptide E285-W323, which contains one potential N-glycosylation site and two C residues that may be disulfide-linked, will be the first tested. The 39-amino acid residue peptide will be synthesized by the University of Florida peptide synthesis facility. The free peptide and the peptide coupled to polylysine will be used as immunogens. The monoclonal antibody facility will immunize five mice with each immunogen. Antibody titers will be measured by ELISA. Typically, one of a group of five mice is superior in terms of antibody response (titer and affinity) and provides a basis for choosing which mouse to use for preparing hybridomas.

Antibody isotype will be determined, and octyl glucoside-treated homogenate of human kidney cortex (from the National Disease Research Interchange/Human Biological Data Interchange, NDRI) will be used for SDS-PAGE and western blotting. The homogenate will also be used for protein A-Sepharose immunoprecipitation of AmP. Part of the immunoprecipitate will be denatured and subjected to SDS-PAGE to examine for the expected Mr 90,000 protein. The remainder will be packed

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into a small column and then washed with 0.1 M ethanolamine to separate native AmP from antibody (113). The eluted protein will be examined for AmP catalytic activity using Arg-Pro-Pro-[^{3}H]benzylamide as substrate (21). The goal is to obtain a specific antibody capable of binding human AmP at an affinity sufficiently high to enable immunocytochemistry studies and immunoaffinity purifications of native AmP from a range of human tissue sources. The immediate work plan focuses largely on determining cellular and subcellular dispositions of AmP. Longer term, the antibodies to AmP will be useful for other purposes such as epidemiologic surveys for AmP deficiency states (62). The first immunogen, E285-W323, contains a tyrosine residue and could therefore be readily labeled with ^{125}I for development of a competitive radioimmunoassay for AmP. If the first peptide immunogen fails to yield an antibody capable of immunoprecipitating native human AmP, one will prepare alternative antigenic sequences; in order of predicted high scores: T38-T51, P582-R597 and (if needed) L568-K578.

For the reasons stated above, one prefers to use relatively small antigenic, unique peptide sequences for preparing anti-AmP. If necessary, however, one will use recombinant wild-type human kidney AmP to prepare a large peptide antigen. The N-terminal third of AmP is unique in comparison with sequences of other members of the 'pita bread" protein family (59). Thus, it should be possible to prepare a specific anti-AmP by using as immunogen the N-piece of AmP formed by acid hydrolysis of the D157-P158 bond. When anti-human AmP becomes available, one will prepare an immunoaffinity chromatography matrix (32) to obtain pure native AmP from kidney and other tissues. Native human kidney AmP will be compared with recombinant wild-type AmP.

Antibodies will be purified on DE-52 cellulose (5,6). As necessary, specific anti-AmP will be immunoabsorbed on antigen covalently bound on Sepharose or the original peptide synthesis resin and then eluted with 0.1 M ethanolamine (32,113). Initially, one will use second antibody conjugates for immunocytochemical studies. However, it has been argued that

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crosslinking of primary antibodies by second antibodies may cause cell membrane antigens to move into caveolae (143,145,153). If the subcellular localization AmP appears to be influenced by second antibody, one will conjugate AmP directly. In our previous studies of the subcellular distribution of angiotensin converting enzyme (ACE), one developed means of conjugating anti-ACE to octapeptide microperoxidase via a bifunctional active ester (6). The same labeling procedure will be used for anti-AmP.

Cellular and subcellular dispositions of AmP.

Immunocytochemistry studies at the level of light microscopy were described above. A major objective now is to define the dispositions of human AmP at the cellular and subcellular levels. The need for high resolution studies can be illustrated as follows: Light micrographs of lung tissue indicate that anti-AmP is captured at sites throughout the alveolar-capillary unit and on endothelium of small arteries and veins. The high resolution of electron microscopy is required to define the actual cellular and subcellular disposition(s) of AmP.

In addition to the need to distinguish which of the cell-types of the alveolar capillary unit possess AmP, there are two other questions raised by our light microscopy studies. Unlike pulmonary ACE, which is disposed on endothelium, one has detected AmP immunoreactivity in association with airway epithelial cells and mononuclear leukocytes. Thus, EM studies are needed to identify the host epithelial cells and leukocytes and to determine whether AmP is disposed on or within the cells. Anticipating that glutaraldehyde-based fixatives may mask AmP epitopes (as was the case for ACE; 5), one conducted all of the light microscopy immunocytochemical studies using fresh tissues (frozen sections) and tissues fixed in picric acid/paraformaldehyde; a fixative adequate for moderately high resolution electron microscopy (5,6). Further one showed that the apparent dispositions of AmP epitopes were not changed by fixation, and one showed that mouse monoclonal anti-AmP (HL510) was not inferior to mouse polyclonal anti-AmP for our immunocytochemical purposes. One can therefore proceed from light microscopy studies directly to EM immunocytochemistry of

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human tissues using picric acid/paraformaldehyde-fixed tissues reacted with monoclonal anti-AmP HL510 (IgG_1 isotype). Antibodies to human AmP antigenic amino acid sequences (see above) will be prepared for final studies. Initially, one will use second antibody conjugates as markers (conjugates of rabbit anti-mouse IgG_1 and, separately, goat anti-mouse IgG_1). The second antibodies will be labeled with colloidal gold (5 or 20 nm) (Goldmark), and reacted tissues will then be prepared for EM as one have described elsewhere (5,6). Alternatively, primary antibodies labeled with 5 or 20 nm colloidal gold can be used. Negative controls will include omission of anti-AmP and substitution of the specific antibody with mouse IgG_1 anti-theophylline (the latter irrelevant antibody to examine for Fc receptors). Anti-AmP previously saturated with AmP will also be used. Positive controls will include use, as the first antibody, monoclonal mouse anti-ACE (an IgM) and polyclonal rabbit anti-fibronectin (30).

The positive control studies will provide a basis for comparison of the disposition(s) of AmP with a marker known to occur on the luminal surface of endothelium (ACE) and with a marker known to be disposed in large part in the extracellular matrix (fibronectin). AmP is believed to be disposed in part on the endothelial surface (31,34,39,44,46). In addition, AmP is believed to be among the enzymes that degrade collagen fragments produced by collagenase (165,204,205); thus, some AmP may be disposed near collagen matrix. To label AmP and fibronectin in the same experiment, one will use two differently conjugated second antibodies; e.g., rabbit anti-mouse IgG_1-5nm colloidal gold for AmP and goat anti-rabbit IgG-20 nm colloidal gold (Zymed) for fibronectin. In addition to the monoclonal anti-ACE noted above, one have a polyclonal rabbit anti-ACE that will be used similarly for the co-localizations of AmP and ACE.

Our mouse anti-guinea pig AmP binds human AmP (32), but at relatively low affinity. The polyclonal mouse anti-human AmP is expected to have a much higher affinity, and one or more of the monoclonal antibodies may as well. Immunocytochemical localizations of AmP will use human tissues (from NDRI); kidney, small intestine, liver, heart, lymphocytes,

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platelets, bone marrow and lungs fresh-fixed in picric acid/paraformaldehyde. Similarly, Clonetics also supplies human renal proximal tubule epithelial cells and endothelial cells from aorta, pulmonary artery and lung microvasculature, all of which one will use for comparison studies.

Cells in culture provide special opportunities for EM immunocytochemistry. As shown previously, cells in monolayer culture can be examined in cross section and as whole cell mounts (10). For example, one showed using cross sections that calmodulin is disposed in endothelial caveolae. By high voltage EM of permeabilized whole endothelial cells viewed on face, calmodulin was found disposed in tracts of caveolae, along microfiloments and in cleavage furrows of dividing cells. Thus, using renal proximal tubule epithelial and vascular endothelial cells in culture, one can localize AmP bound to cell membrane and/or disposed in intracellular compartments. If, in fact, soluble forms of AmP are reactive with our anti-human kidney AmP, one should be able to localize AmP within lymphocytes and platelets permeabilized after fixation.

Membrane-bound forms of AmP.

Human kidney cortex will be the first tissue to be examined. Our light microscopy studies indicate that the vast preponderance of renal AmP is associated with renal proximal tubule epithelium, with lesser amounts being distributed on all endothelia except for glomerular endothelium (39). At present, relatively little is known of the subcellular distribution of gpi-anchored proteins on specialized epithelia, thus our findings on the disposition(s) of AmP may be instructive in terms of other gpi-anchored proteins, such as membrane dipeptidase (109,110). For reasons presented above, one expects that most renal AmP will be shown to be an ectoenzyme with its catalytic site oriented to the luminal space. Fixed tissue will also be permeabilized with 1% Triton X-100 to facilitate detection of AmP in intracellular sites (10). Proximal tubule epithelial cells in culture will be examined similarly and tested in addition for AmP catalytic activity. Intact and permeabilized fixed cells will be examined in cross section and en face.

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Endothelial-associated AmP is expected to be disposed as an ectoenzyme and, as a gpi-anchored protein, may be disposed largely in caveolae (121,171,175).

AmP appears by light microscopy (39) to be disposed on brush border epithelium and endothelium of the villus vascular core of the small intestine. Lung tissue will be examined next, as described above. Separately, fixed cultures of endothelial cells from aorta, pulmonary artery and lung microvasculature (all from Clonetics) will be examined, intact and permeabilized.

Soluble forms of AmP.

It is not yet known whether the soluble forms of AmP that are found in lymphocytes, platelets, neuronal tissues and adrenal medulla (98,147,165,191,192) are alternative products of the same gene that encodes membrane-bound forms. To gain insight into the question, one will attempt immunoprecipitation of these soluble AmPs using antibodies to human kidney AmP (see above). Clearly, if the immunoprecipitations are successful, one will have a basis for proceeding to immunocytochemical localization using the target tissues fixed and permeabilized. As a further step, one will examine poly A RNAs of lymphocytes and adrenal medulla by RT-PCR using nested primers designed from kidney AmP cDNA. The sense and antisense primers will be selected to cover sequence from just upstream of the putative proton shuttle (H430) to a downstream site just 3′ to the last putative metal ligand (E569). The PCR product, if obtained, will be sequenced. If, in fact, lymphocyte and adrenal medulla AmPs are encoded over their putative "pita bread" domains as is kidney AmP, one will (as described above) examine by 3′RACE RT-PCR for alternative C-terminal sequences that may direct soluble AmPs to intracellular sites.

Simmons has reported that human heart AmP is soluble (152), and this may be true for liver AmP as well. However, the possibility is not ruled out that heart and liver contain an abundance of phospholipase C or D that, during the homogenization process, converts amphipathic AmP into a hydrophilic form. Immunocytochemistry studies should help resolve this

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question. Even if soluble and normally stored in intracellular sites, human heart and liver AmP must have a strong structural resemblance to kidney AmP: On Northern blotting using human kidney AmP cDNA that encodes the kidney AmP sequence R123-A478, heart and liver poly A RNAs were found to be highly reactive (47). Further, each had a single message of the size, 3.5kb, of the kidney AmP RNA. If heart and liver AmPs are, in intact tissue, disposed intracellularly, it should be a straightforward matter to identify a C-terminal sequence signal that directs cell retention.

Membrane-bound AmP and its nearest neighbors.

Reactions at the cell surface can set off a cascade of secondary, tertiary and higher reactions that are determined in part by the physical proximity and fit of downstream protein reactants. Receptor activation and subsequent cell signaling is perhaps the clearest example (63,74,130,137,142), especially for receptors with seven transmembrane domains with intracellular peptide loops, one or more of which can be phosphorylated and dephosphorylated (63). There is an abundant and growing literature describing close chemical and biochemical associations between ligand-bound receptors, signaling molecules and caveolins (e.g. see 92,130,131,137,138,160,171,173,175,183). An objective in this subproject is to develop morphologic means of documenting close anatomical associations of functionally-related molecules.

Increasingly, it appears that reactions involving cell surface gpi-anchored proteins can also set off a cascade of events. Gpi-anchored T-cell receptor is coupled to Src-family kinases (142). An insulin-dependent gpi-anchor hydrolysis has been described and leads to generation of inositol phosphoglycan (IPG) second messengers (142). Purified IPGs alone can mimic insulin activities. Through the same, or a parallel pathway, insulin stimulates a tyrosine phosphorylation of caveolin (142).

Previously, it was shown that bradykinin (BK), in concentrations as low as 10 pM, causes endothelial cells to mobilize arachidonate, some of which is converted into thromboxane A_2 (8-11). Des-Arg^1-BK, the product formed by AmP, is the only lower homolog of BK, in a near-comparable

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concentration, capable of mobilizing endothelial arachidonate. Possibly of relevance, des-Arg^1-BK has as great an affinity for AmP as BK itself. It is a tenable speculation that a BK-dependent gpi-anchor hydrolysis exists, a gpi-anchor at issue is that of AmP, and part or all of the arachidonate mobilized comes from the diacylglycerol formed by gpi-anchor hydrolysis. In these terms, BK may exert some of its effects via AmP.

It is now widely believed that most of the biological effects of BK are initiated by activation of the B2 receptor and are mediated through calmodulin-dependent eNOS and guanylate cyclase (see 63 and its references). If, as expected, endothelial AmP is largely restricted to caveolae, it is well-positioned for at least indirect linkage with eNOS and guanylate cyclase, which appear to be largely disposed on the cytoplasmic aspect of caveolae (92,131). Endothelial cells respond to BK as if they have B2 receptors; however the subcellular dispositions of B2 receptors have, to our knowledge, never been defined at the level of electron microscopy.

If, in fact, binding of BK to the B2 receptor activates eNOS and guanylate cyclase (as opposed to binding of BK to an alternative effector), the B2 receptor is likely in very close physical proximity. Our immediate objective here is to develop a novel perspective on how BK exerts effects on endothelium by helping to define nearest-neighbors of AmP and the B2 receptors. Such data as are available indicate that the B2 receptor is situated on or within a cell membrane microdomain, perhaps in caveolae, that can be rapidly taken up by endocytosis (63).

It is proposed to use endothelial cell plasma membrane/caveolae fractions prepared as described previously (3,4,8,11). In brief, post-confluent endothelial cells in culture (which contain caveolae in large numbers (7,8,10,11)) will be harvested with a rubber spatula, homogenized, and then centrifuged to remove nuclei and cell debris. The supernatant will then be reacted with 5′-adenosine monophosphate (5′-AMP) in the presence of lead nitrate. Caveolar 5′-AMPase, a gpi-anchored protein, hydrolyzes 5′-AMP to form adenosine and Pi. Pi is precipitated as lead phosphate within caveolae and thereby greatly increases the density of the plasma

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membrane/caveolae fraction. The latter fraction is then easily separated from soluble proteins and other membrane systems by low g-force (~100xg) centrifugation of the reaction mixture through a relatively dense sucrose cushion (4). Remarkably, about 65% of the 5'-AMPase remains active, and angiotensin converting enzyme (3,4) and AmP activities (unpublished) are readily measured.

The resulting endothelial cell membrane/caveolae "ghosts" provide a number of advantages for our present purposes. Firstly, antigenic sites on both the extracellular and cytoplasmic aspects of the cell membrane are accessible to added antibodies. Secondly, the fraction contains both "unspecialized" cell membrane and attached caveolae. Should, contrary to expectations, the B2 receptor be disposed at sites outside of caveolae, one will find these sites. Thirdly, when of interest, the plasma membrane/caveolae fraction can be treated with Triton X-100 to form its Triton-soluble and Triton-insoluble subfractions (150,175). AmP and 5'-AMPase are expected to be enriched in the Triton-insoluble particulate.

One can use a rabbit anti-human B2 receptor that binds to a cytoplasmic epitope of the B2 receptor, C361-Q395 (63). One or more of the serines of C361-Q395 is phosphorylated when the B2 receptor of human foreskin fibroblasts is reacted with BK (63). With our mouse anti-AmP and rabbit anti-B2 receptor preparations, one can localize the target antigens on human endothelial cell (Clonetics) plasma membrane/caveolae fractions using anti-mouse IgG conjugated to 5 nm colloidal gold and anti-rabbit IgG conjugated to 20 nm colloidal gold. If second antibody places gold particles too distant for assigning antigen sites, we will label primary antibodies (6).

By the same approach, one can define the subcellular dispositions of AmP and the B2 receptor in respect to dispositions of eNOS and guanylate cyclase (using commercially-available anti-eNOS and anti-guanylate cyclase). Our aim is to develop and document a morphologic approach to complement biochemical data already in hand on the apparently tight physical association of signal transduction molecules believed to be disposed in association with caveolae (e.g. see 89,90,92,130,131,160,173). In

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addition, our approach should also help clarify anatomic associations between proteins disposed on the extracellular aspect of the plasma membrane with functionally-linked counterparts disposed on the cytoplasmic aspect.

Success in this subproject can be exploited by us and others in terms of relating morphologically a host of other proteins of interest, including (but not limited to) the caveolins, Ca^{2+}-ATPase, the IP_3 receptor, adenosine and prostaglandin transporters and heterotrimeric G proteins (90,130,132,137,173,184).

Alternative Splicing.

Complementary DNA clones encoding human membrane-bound AmP were isolated by reverse transcription-polymerase chain reaction (RT-PCR) of human kidney and lung poly(A)+ RNA. Northern hybridization analysis and RT-PCR suggests that the soluble and membrane-bound forms of human AmP are products of two distinct mRNAs which may be produced through alternative splicing, have different C-terminal sequences. Intronic sequences involved in such alternative splicing can be included in human AmP constructs to allow production of both forms of human AmP. In such constructs, it is preferred that sequences from only the specific introns involved in the alternative splicing be used. Such a construct is thus a cDNA/genomic hybrid construct, containing both cDNA and genomic DNA. The cDNA portion of such a construct lacks intronic sequences which are present in corresponding genomic sequences.

Construction of Transgenic Animals.

Animal Sources.

Animals suitable for transgenic experiments can be obtained from standard commercial sources such as Charles River (Wilmington, MA), Taconic (Germantown, NY), and Harlan Sprague Dawley (Indianapolis, IN). Many strains are suitable, but Swiss Webster (Taconic) female mice are preferred for embryo retrieval and transfer. $B6D2F_1$ (Taconic) males can be used for mating and vasectomized Swiss Webster studs can be used to

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stimulate pseudopregnancy. Vasectomized mice and rats can be obtained from the supplier.

Microinjection Procedures.

The procedures for manipulation of the rodent embryo and for microinjection of DNA are described in detail in Hogan *et al.*, *Manipulating the Mouse Embryo* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1986), the teachings of which are incorporated herein.

Transgenic Mice.

Female mice six weeks of age are induced to superovulate with a 5 IU injection (0.1 cc, ip) of pregnant mare serum gonadotropin (PMSG; Sigma) followed 48 hours later by a 5 IU injection (0.1 cc, ip) of human chorionic gonadotropin (hCG; Sigma). Females are placed with males immediately after hCG injection. Twenty-one hours after hCG injection, the mated females are sacrificed by CO_2 asphyxiation or cervical dislocation and embryos are recovered from excised oviducts and placed in Dulbecco's phosphate buffered saline with 0.5% bovine serum albumin (BSA; Sigma). Surrounding cumulus cells are removed with hyaluronidase (1 mg/ml). Pronuclear embryos are then washed and placed in Earle's balanced salt solution containing 0.5% BSA (EBSS) in a 37.5°C incubator with a humidified atmosphere at 5% CO_2, 95% air until the time of injection. Embryos can be implanted at the two cell stage.

Randomly cycling adult female mice are paired with vasectomized males. Swiss Webster or other comparable strains can be used for this purpose. Recipient females are mated at the same time as donor females. At the time of embryo transfer, the recipient females are anesthetized with an intraperitoneal injection of 0.015 ml of 2.5% avertin per gram of body weight. The oviducts are exposed by a single midline dorsal incision. An incision is then made through the body wall directly over the oviduct. The ovarian bursa is then torn with watchmakers forceps. Embryos to be transferred are placed in DPBS (Dulbecco's phosphate buffered saline) and in the tip of a transfer pipet (about 10 to 12 embryos). The pipet tip is inserted

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into the infundibulum and the embryos transferred. After the transfer, the incision is closed by two sutures.

Transgenic Rats.

The procedure for generating transgenic rats is similar to that of mice (Hammer *et al.*, *Cell* 63:1099-112 (1990)). Thirty day-old female rats are given a subcutaneous injection of 20 IU of PMSG (0.1 cc) and 48 hours later each female placed with a proven male. At the same time, 40-80 day old females are placed in cages with vasectomized males. These will provide the foster mothers for embryo transfer. The next morning females are checked for vaginal plugs. Females who have mated with vasectomized males are held aside until the time of transfer. Donor females that have mated are sacrificed (CO_2 asphyxiation) and their oviducts removed, placed in DPBS (Dulbecco's phosphate buffered saline) with 0.5% BSA and the embryos collected. Cumulus cells surrounding the embryos are removed with hyaluronidase (1 mg/ml). The embryos are then washed and placed in EBSS (Earle's balanced salt solution) containing 0.5% BSA in a 37.5°C incubator until the time of microinjection.

Once the embryos are injected, the live embryos are moved to DPBS for transfer into foster mothers. The foster mothers are anesthetized with ketamine (40 mg/kg, ip) and xylazine (5 mg/kg, ip). A dorsal midline incision is made through the skin and the ovary and oviduct are exposed by an incision through the muscle layer directly over the ovary. The ovarian bursa is torn, the embryos are picked up into the transfer pipet, and the tip of the transfer pipet is inserted into the infundibulum. Approximately 10 to 12 embryos are transferred into each rat oviduct through the infundibulum. The incision is then closed with sutures, and the foster mothers are housed singly.

Embryonic Stem (ES) Cell Methods.

Introduction of DNA into ES cells.

Methods for the culturing of ES cells and the subsequent production of transgenic animals, the introduction of DNA into ES cells by a variety of methods such as electroporation, calcium phosphate/DNA precipitation, and direct injection are described in detail in *Teratocarcinomas and Embryonic*

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Stem Cells, A Practical Approach, ed. E.J. Robertson, (IRL Press 1987), the teachings of which are incorporated herein. Selection of the desired clone of transgene-containing ES cells can be accomplished through one of several means. For random gene integration, an AmP clone is co-precipitated with a gene encoding neomycin resistance. Transfection is carried out by one of several methods described in detail in Lovell-Badge, in *Teratocarcinomas and Embryonic Stem Cells, A Practical Approach*, ed. E.J. Robertson, (IRL Press 1987), or in Potter *et al.*, *Proc. Natl. Acad. Sci. USA* 81:7161 (1984). Lipofection can be performed using reagents such as provided in commercially available kits, for example DOTAP (Boehringer-Mannheim) or lipofectin (BRL). Calcium phosphate/DNA precipitation, lipofection, direct injection, and electroporation are the preferred methods. In these procedures, 0.5 X 10^6 ES cells are plated into tissue culture dishes and transfected with a mixture of the linearized AmP clone and 1 mg of pSV2neo DNA (Southern and Berg, *J. Mol. Appl. Gen.* 1:327-341 (1982)) precipitated in the presence of 50 mg lipofectin (BRL) in a final volume of 100 µl. The cells are fed with selection medium containing 10% fetal bovine serum in DMEM supplemented with G418 (between 200 and 500 µg/ml). Colonies of cells resistant to G418 are isolated using cloning rings and expanded. DNA is extracted from drug resistant clones and Southern blots using an AmP cDNA probe can be used to identify those clones carrying the AmP sequences. PCR detection methods may also used to identify the clones of interest.

DNA molecules introduced into ES cells can also be integrated into the chromosome through the process of homologous recombination, described by Capecchi (1989). Direct injection results in a high efficiency of integration. Desired clones can be identified through PCR of DNA prepared from pools of injected ES cells. Positive cells within the pools can be identified by PCR subsequent to cell cloning (Zimmer and Gruss, *Nature* 338:150-153 (1989). DNA introduction by electroporation is less efficient and requires a selection step. Methods for positive selection of the recombination event (for example, neo resistance) and dual positive-negative

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selection (for example, neo resistance and gancyclovir resistance) and the subsequent identification of the desired clones by PCR have been described by Joyner *et al.*, *Nature* 338:153-156 (1989), and Capecchi (1989), the teachings of which are incorporated herein.

Embryo Recovery and ES cell Injection.

Naturally cycling or superovulated female mice mated with males can be used to harvest embryos for the implantation of ES cells. It is desirable to use the C57BL/6 strain for this purpose when using mice. Embryos of the appropriate age are recovered approximately 3.5 days after successful mating. Mated females are sacrificed by CO_2 asphyxiation or cervical dislocation and embryos are flushed from excised uterine horns and placed in Dulbecco's modified essential medium plus 10% calf serum for injection with ES cells. Approximately 10 to 20 ES cells are injected into blastocysts using a glass microneedle with an internal diameter of approximately 20 μm.

Transfer of Embryos to Pseudopregnant Females.

Randomly cycling adult female mice are paired with vasectomized males. Mouse strains such as Swiss Webster, ICR or others can be used for this purpose. Recipient females are mated such that they will be at 2.5 to 3.5 days post-mating when required for implantation with blastocysts containing ES cells. At the time of embryo transfer, the recipient females are anesthetized with an intraperitoneal injection of 0.015 ml of 2.5% avertin per gram of body weight. The ovaries are exposed by making an incision in the body wall directly over the oviduct and the ovary and uterus are externalized. A hole is made in the uterine horn with a 25 gauge needle through which the blastocysts are transferred. After the transfer, the ovary and uterus are pushed back into the body and the incision is closed by two sutures. This procedure is repeated on the opposite side if additional transfers are to be made.

Identification, Characterization, and Utilization of Transgenic Mice and Rats.

Transgenic rodents can be identified by analyzing their DNA. For

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this purpose, tail samples (1 to 2 cm) can be removed from three week old animals. DNA from these or other samples can then be prepared and analyzed by Southern blot, PCR, or slot blot to detect transgenic founder (F_0) animals and their progeny (F_1 and F_2).

Disclosed is an isolated nucleic acid molecule encoding the amino acid sequence shown in SEQ ID NO:2, or a fragment of at least six amino acids of the amino acid sequence shown in SEQ ID NO:2. Preferably the nucleic acid molecule includes expression sequences, at least one intron, or both. Preferred forms of the nucleic acid molecule are SEQ ID NO:1, SEQ ID NO:6, and nucleotides 1 to 29,271 of SEQ ID NO:6. Also disclosed are fragments of SEQ ID NO:1, or fragments of the collective sequence represented by SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7 (the genomic sequence). It is preferred that the fragments contain at least 10 nucleotides, at least 15 nucleotides, at least 18 nucleotide, or at least 20 nucleotides. Also disclosed are aminopeptidase P regulatory sequences present SEQ ID NOs:3, 4, 5, 6, and 7. A preferred regulatory sequence is a fragment of SEQ ID NO:5 that promotes transcription of a nucleic acid segment operatively linked to the fragment.

Also disclosed are proteins having the amino acid sequence shown in SEQ ID NO:2 or a variant amino acid sequence where one or more amino acids shown in SEQ ID NO:2 are replaced with a conservative substitute amino acid. A preferred form of the protein has from one to ten amino acids shown in SEQ ID NO:2 are replaced with a conservative substitute amino acid. Also disclosed are proteins including a portion of the amino acid sequence shown in SEQ ID NO:2 such that the protein is soluble in aqueous solution (also referred to as soluble aminopeptidase P). A protein having the amino acid sequence shown in SEQ ID NO:2 or a variant amino acid sequence, where the protein has aminopeptidase activity. Also disclosed are peptides including a fragment of at least six amino acids of the amino acid sequence shown in SEQ ID NO:2. Also disclosed are antibodies reactive with the disclosed proteins or peptides.

Also disclosed is a method of detecting aminopeptidase P mutants

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performed by comparing all or a part of a nucleotide sequence encoding aminopeptidase P with the corresponding nucleotide sequence of SEQ ID NO:1, or the collective nucleotide sequence represented by SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7. Also disclosed is a method of identifying a compound that inhibits aminopeptidase P by bringing into contact cells and a compound to be tested, measuring the level of aminopeptidase P activity in the cells, and comparing the measured level of activity with the level of activity in cells not brought into contact with the compound to be tested. Also disclosed is a method of identifying a compound that inhibits aminopeptidase P expression by bringing into contact cells expressing aminopeptidase and a compound to be tested, measuring the level of aminopeptidase P expression in the cells, and comparing the measured level of expression with the level of expression in cells not brought into contact with the compound to be tested.

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Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

BNSDOCID: <WO___9911799A2_I_>

We claim:

1. An isolated nucleic acid molecule encoding the amino acid sequence shown in SEQ ID NO:2, or a fragment of at least six amino acids of the amino acid sequence shown in SEQ ID NO:2.

2. The nucleic acid molecule of claim 1 wherein the nucleic acid molecule comprises at least one intron.

3. The nucleic acid molecule of claim 1 wherein the nucleic acid molecule comprises expression sequences.

4. The nucleic acid molecule of claim 1 comprising SEQ ID NO:1.

5. The nucleic acid molecule of claim 1 comprising nucleotides 1 to 29,271 of SEQ ID NO:6.

6. A protein comprising the amino acid sequence shown in SEQ ID NO:2 or a variant amino acid sequence where one or more amino acids shown in SEQ ID NO:2 are replaced with a conservative substitute amino acid.

7. The protein of claim 6 wherein from one to ten amino acids shown in SEQ ID NO:2 are replaced with a conservative substitute amino acid.

8. An antibody reactive with the protein of claim 6.

9. A protein comprising a portion of the amino acid sequence shown in SEQ ID NO:2 such that the protein is soluble in aqueous solution.

10. A protein comprising the amino acid sequence shown in SEQ ID NO:2 or a variant amino acid sequence, wherein the protein has aminopeptidase activity.

11. A peptide comprising a fragment of at least six amino acids of the amino acid sequence shown in SEQ ID NO:2.

12. An antibody reactive with the peptide of claim 11.

13. A nucleic acid molecule comprising a fragment of SEQ ID NO:1, or a fragment of the collective sequence represented by SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, wherein the fragment comprises at least 10 nucleotides.

14. The nucleic acid molecule of claim 13 wherein the fragment comprises at least 15 nucleotides.

BNSDOCID <WO___9911799A2_I_>

15. The nucleic acid molecule of claim 13 wherein the fragment comprises at least 20 nucleotides.

16. A nucleic acid molecule comprising a fragment of SEQ ID NO:5 wherein the fragment promotes transcription of a nucleic acid segment operatively linked to the fragment.

17. A method of detecting aminopeptidase P mutants comprising comparing all or a part of a nucleotide sequence encoding aminopeptidase P with the corresponding nucleotide sequence of SEQ ID NO:1, or the collective nucleotide sequence represented by SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

18. A method of identifying a compound that inhibits aminopeptidase P, the method comprising bringing into contact cells and a compound to be tested, measuring the level of aminopeptidase P activity in the cells, and comparing the measured level of activity with the level of activity in cells not brought into contact with the compound to be tested.

19. A method of identifying a compound that inhibits aminopeptidase P expression, the method comprising bringing into contact cells expressing aminopeptidase and a compound to be tested, measuring the level of aminopeptidase P expression in the cells, and comparing the measured level of expression with the level of expression in cells not brought into contact with the compound to be tested.

BNSDOCID: <WO___9911799A2_I_>

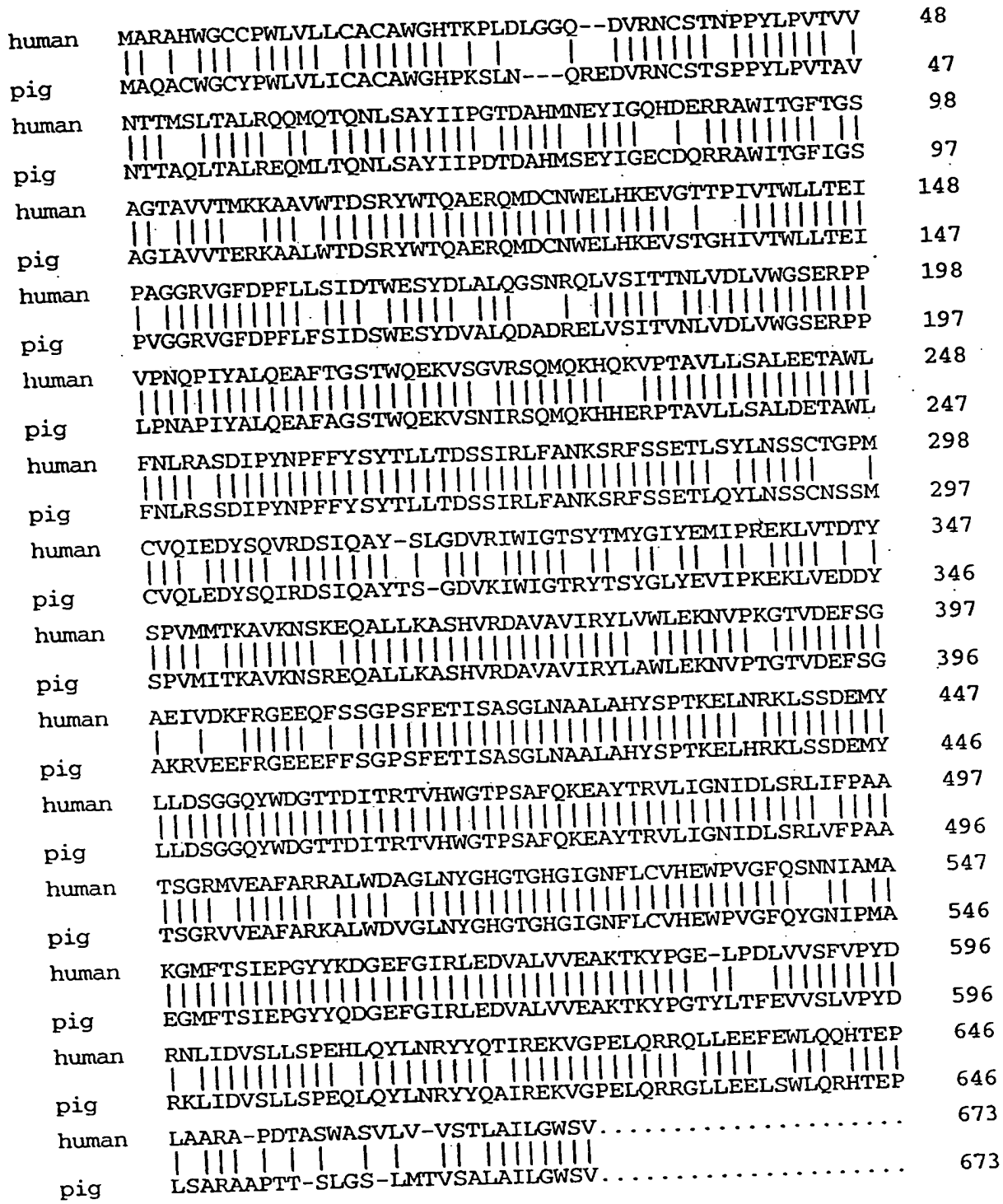

FIGURE 1

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gag aaa gta tct ggc gtc cga agc cag atg cag aag cat caa aag gtc   963
Glu Lys Val Ser Gly Val Arg Ser Gln Met Gln Lys His Gln Lys Val
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ccg act gcc gtc ctt ctg tcg gcg ctt gag gag acg gcc tgg ctc ttc  1011
Pro Thr Ala Val Leu Leu Ser Ala Leu Glu Glu Thr Ala Trp Leu Phe
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aac ctt cga gcc agt gac atc ccc tat aac ccc ttc ttc tat tcc tac  1059
Asn Leu Arg Ala Ser Asp Ile Pro Tyr Asn Pro Phe Phe Tyr Ser Tyr
250                 255                 260                 265

acg ctg ctc aca gac tct tct att agg ttg ttt gca aac aag agt cgc  1107
Thr Leu Leu Thr Asp Ser Ser Ile Arg Leu Phe Ala Asn Lys Ser Arg
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ttt agc tcc gaa acc ttg agc tat ctg aac tcc agt tgc aca ggc ccc  1155
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gcc tac tca ttg gga gat gtg agg atc tgg att ggg acc agc tat acc   1251
Ala Tyr Ser Leu Gly Asp Val Arg Ile Trp Ile Gly Thr Ser Tyr Thr
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Met Tyr Gly Ile Tyr Glu Met Ile Pro Arg Glu Lys Leu Val Thr Asp
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acc tac tcc cca gtg atg atg acc aag gca gtg aag aac agc aag gag   1347
Thr Tyr Ser Pro Val Met Met Thr Lys Ala Val Lys Asn Ser Lys Glu
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Gln Ala Leu Leu Lys Ala Ser His Val Arg Asp Ala Val Ala Val Ile
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cgg tac ttg gtc tgg ctg gag aag aac gtg ccc aaa ggc aca gtg gat   1443
Arg Tyr Leu Val Trp Leu Glu Lys Asn Val Pro Lys Gly Thr Val Asp
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gag ttt tcg ggg gca gag atc gtg gac aag ttc cga gga gaa gaa cag   1491
Glu Phe Ser Gly Ala Glu Ile Val Asp Lys Phe Arg Gly Glu Glu Gln
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Phe Ser Ser Gly Pro Ser Phe Glu Thr Ile Ser Ala Ser Gly Leu Asn
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gct gcc ctg gcc cac tac agc ccg acc aag gag ctg aac cgc aag ctg   1587
Ala Ala Leu Ala His Tyr Ser Pro Thr Lys Glu Leu Asn Arg Lys Leu
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tcc tca gat gag atg tac ctg ctg gac tct ggg ggg cag tac tgg gac   1635
Ser Ser Asp Glu Met Tyr Leu Leu Asp Ser Gly Gly Gln Tyr Trp Asp
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ggg acc aca gac atc acc aga aca gtc cac tgg ggc acc ccc tct gcc   1683
Gly Thr Thr Asp Ile Thr Arg Thr Val His Trp Gly Thr Pro Ser Ala
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Phe Gln Lys Glu Ala Tyr Thr Arg Val Leu Ile Gly Asn Ile Asp Leu
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tcc agg ctc atc ttt ccc gct gct aca tca ggg cga atg gtg gag gcc   1779
Ser Arg Leu Ile Phe Pro Ala Ala Thr Ser Gly Arg Met Val Glu Ala
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Phe Ala Arg Arg Ala Leu Trp Asp Ala Gly Leu Asn Tyr Gly His Gly
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Gly Phe Gln Ser Asn Asn Ile Ala Met Ala Lys Gly Met Phe Thr Ser
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att gaa cct ggt tac tat aag gat gga gaa ttt ggg atc cgt ctc gaa   1971
Ile Glu Pro Gly Tyr Tyr Lys Asp Gly Glu Phe Gly Ile Arg Leu Glu
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gat gtg gct ctc gtg gta gaa gca aag acc aag tac cca ggg gag cta   2019
Asp Val Ala Leu Val Val Glu Ala Lys Thr Lys Tyr Pro Gly Glu Leu
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cct gac ctt gtg gta tca ttt gtg ccc tat gac cgg aac ctc atc gat   2067
Pro Asp Leu Val Val Ser Phe Val Pro Tyr Asp Arg Asn Leu Ile Asp
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gtc agc ctg ctg tct ccc gag cat ctc cag tac ctg aat cgc tac tac   2115
Val Ser Leu Leu Ser Pro Glu His Leu Gln Tyr Leu Asn Arg Tyr Tyr
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cag acc atc cgg gag aag gtg ggt cca gag ctg cag agg cgc cag cta   2163
Gln Thr Ile Arg Glu Lys Val Gly Pro Glu Leu Gln Arg Arg Gln Leu
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cta gag gag ttc gag tgg ctt caa cag cac aca gag ccc ctg gcc gcc   2211
Leu Glu Glu Phe Glu Trp Leu Gln Gln His Thr Glu Pro Leu Ala Ala
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agg gcc cca gac acc gcc tcc tgg gcc tct gtg tta gtg gtc tcc acc   2259
Arg Ala Pro Asp Thr Ala Ser Trp Ala Ser Val Leu Val Val Ser Thr
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Val Arg Asn Cys Ser Thr Asn Pro Pro Tyr Leu Pro Val Thr Val Val
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Asn Thr Thr Met Ser Leu Thr Ala Leu Arg Gln Gln Met Gln Thr Gln
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Asn Leu Ser Ala Tyr Ile Ile Pro Gly Thr Asp Ala His Met Asn Glu
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Tyr Ile Gly Gln His Asp Glu Arg Arg Ala Trp Ile Thr Gly Phe Thr
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Gly Ser Ala Gly Thr Ala Val Val Thr Met Lys Lys Ala Ala Val Trp
            100                 105                 110

Thr Asp Ser Arg Tyr Trp Thr Gln Ala Glu Arg Gln Met Asp Cys Asn
        115                 120                 125

Trp Glu Leu His Lys Glu Val Gly Thr Thr Pro Ile Val Thr Trp Leu
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Ser Gln Met Gln Lys His Gln Lys Val Pro Thr Ala Val Leu Leu Ser
225 230 235 240

Ala Leu Glu Glu Thr Ala Trp Leu Phe Asn Leu Arg Ala Ser Asp Ile
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Pro Tyr Asn Pro Phe Phe Tyr Ser Tyr Thr Leu Leu Thr Asp Ser Ser
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Ile Arg Leu Phe Ala Asn Lys Ser Arg Phe Ser Ser Glu Thr Leu Ser
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Ala Thr Ser Gly Arg Met Val Glu Ala Phe Ala Arg Arg Ala Leu Trp
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Asp Ala Gly Leu Asn Tyr Gly His Gly Thr Gly His Gly Ile Gly Asn
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Phe Leu Cys Val His Glu Trp Pro Val Gly Phe Gln Ser Asn Asn Ile
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Ala Met Ala Lys Gly Met Phe Thr Ser Ile Glu Pro Gly Tyr Tyr Lys
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Asp Gly Glu Phe Gly Ile Arg Leu Glu Asp Val Ala Leu Val Val Glu
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Ala Lys Thr Lys Tyr Pro Gly Glu Leu Pro Asp Leu Val Val Ser Phe
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Val Pro Tyr Asp Arg Asn Leu Ile Asp Val Ser Leu Leu Ser Pro Glu
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His Leu Gln Tyr Leu Asn Arg Tyr Tyr Gln Thr Ile Arg Glu Lys Val
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Gly Pro Glu Leu Gln Arg Arg Gln Leu Leu Glu Glu Phe Glu Trp Leu
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Gln Gln His Thr Glu Pro Leu Ala Ala Arg Ala Pro Asp Thr Ala Ser
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(57) Abstract

Disclosed are the human aminopeptidase P cDNA and genomic DNA. Also disclosed is the human aminopeptidase P protein and antibodies reactive with human aminopeptidase P. These molecules, and derivatives of these molecules, are useful for assay for detecting aminopeptidase polymorphisms, protein variants, and activity, and identifying compounds that inhibit expression of aminopeptidase genes and activity of aminopeptidase protein.

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BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
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CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
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CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

BNSDOCID: <WO___9911799A3_I_>

INTERNATIONAL SEARCH REPORT

Ir ational Application No
PCT/US 98/18426

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/57 C12N9/48 C07K16/40 C12Q1/68 C12Q1/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C12Q C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	VENEMA, RICHARD C. ET AL: "Cloning and tissue distribution of human membrane-bound aminopeptidase P." BIOCHIMICA ET BIOPHYSICA ACTA, (OCT. 9, 1997) VOL. 1354, NO. 1, PP. 45-48 ISSN: 0006-3002., XP002095023 see the whole document ---	1-19
X	HYDE, RALPH J. ET AL: "Molecular cloning and expression in COS-1 cells of pig kidney aminopeptidase P." BIOCHEMICAL JOURNAL, (1996) VOL. 319, NO. 1, PP. 197-201. ISSN: 0264-6021., XP002095024 see the whole document ---	1-19

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[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
1 March 1999	16/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hix, R

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/18426

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	SIDOROWICZ W ET AL: "KININ CLEAVAGE BY HUMAN ERYTHROCYTES." AM J HEMATOL, (1984) 17 (4), 383-392. CODEN: AJHEDD. ISSN: 0361-8609., XP002095026 see the whole document ---	1-19
Y	RYAN, J. W. ET AL: "Immunoaffinity purifications of aminopeptidase P from guinea pig lungs, kidney and serum" BIOCHEM. BIOPHYS. RES. COMMUN. (1994), 205(3), 1796-802 CODEN: BBRCA9;ISSN: 0006-291X,1994, XP002095028 cited in the application see the whole document ---	1-19
Y	LIM, JAESEUNG ET AL: "Chemical modification of porcine kidney aminopeptidase P indicates the involvement of two critical histidine residues." FEBS LETTERS, (1996) VOL. 381, NO. 3, PP. 188-190. ISSN: 0014-5793., XP002095029 see the whole document ---	1-19
Y	LLOYD, GEORGINA S. ET AL: "Inhibition and metal ion activation of pig kidney aminopeptidase P. Dependence on nature of substrate." BIOCHEMICAL PHARMACOLOGY, (1996) VOL. 52, NO. 2, PP. 229-236. ISSN: 0006-2952., XP002095030 see the whole document ---	1-19
Y	H-T. HARBECK ET AL.: "Aminopeptidase P from rat brain." EUR. J. BIOCHEM., vol. 198, no. 2, June 1991, pages 451-458, XP002095031 cited in the application see the whole document ---	1-19
Y	N.M. HOOPER ET AL.: "Purification and characterization of pig kidney aminopeptidase." BIOCHEM. J. , vol. 267, no. 2, 15 April 1990, pages 509-515, XP002095032 cited in the application see the whole document --- -/--	1-19

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	I. RUSU ET AL.: "Aminopeptidase P from human leukocytes." EUR. J. BIOCHEM., vol. 210, no. 1, November 1992, pages 93-100, XP002095033 cited in the application see the whole document	1-19
Y	W.H. SIMMONS ET AL.: "Membrane-bound Aminopeptidase P from Bovine lung." THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 7, 5 March 1992, pages 4897-4903, XP002095034 cited in the application see the whole document	1-19
Y	G. VANHOOF ET AL.: "Kininase activity in human platelets: cleavage of the Arg1-Pro2 bond of bradykinin by Aminopeptidase P." BIOCHEMICAL PHARMACOLOGY, vol. 44, no. 3, 4 August 1992, pages 479-487, XP002095035 cited in the application see the whole document	1-19
A	JU, H. ET AL: "Aminopeptidase P in human tissues: Northern blot analysis." FASEB JOURNAL, (1997) VOL. 11, NO. 3, PP. A504. MEETING INFO.: ANNUAL MEETING OF THE PROFESSIONAL RESEARCH SCIENTISTS ON EXPERIMENTAL BIOLOGY 97 NEW ORLEANS, LOUISIANA, USA APRIL 6-9, 1997 ISSN: 0892-6638., XP002095025 see the whole document	1-19

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